Multicompartment Models of Uptake and Excretion of Chemicals

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MULTICOMPARTMENT MODELS OF UPTAKE AND EXCRETION OF CHEMICALS

by

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ABSTRACT

Zitko, V. 1986. Multicompartment models of uptake and excretion of chemicals. Can. Tech. Rep. Fish. Aquat. Sci. 1421: iii + 8 p. + Appendix.

Two programs for fitting multicompartment models to data on uptake and excretion of chemicals are presented. One uses least squares fit of the rate equations, the other is a simplex search for best fitting rate coefficients of the integrated equations. A simulation program and utilities programs for file manipulation and data plotting are also presented.

RÉSUMÉ

Zitko, V. 1986. Multicompartment models of uptake and excretion of chemicals. Can. Tech. Rep. Fish. Aquat. Sci. 1421: iii + 8 p. + Appendix.

Deux programmes d'ajustement de modèles à plusieurs compartiments à des données sur l'absorption et l'évacuation de produits chimiques sont présentés. Un ajuste les équations de débit aux moindres carrés, l'autre cherche par la méthode du Simplex les meilleures valeurs approchées des coefficients de débit des équations intégrées. Un programme de simulation et des programmes utilitaires de manipulation des fichiers et de traçage des courbes sont aussi présentés.

INTRODUCTION

The one-compartment model (OCM) is used frequently in aquatic toxicology to provide first approximation of uptake and excretion of chemicals by aquatic biota. The advantage of OCM is that it can be fitted relatively easily and the effect of its two parameters (uptake and excretion rate constants, k1 and k2) on the shape of the uptake and excretion curves and on the bioconcentration factor can be readily visualized. Unfortunately, the fit is often not very satisfactory. In addition, OCM cannot be used when chemicals are measured in more than one tissue. A program for fitting two compartment models (TCM) was described recently (Zitko 1982). This report provides programs that can deal with 9-10 compartments and that can be readily modified to accommodate additional compartments (Table 1). This is of interest mostly for simulations since the difficulties of fitting multicompartment models increase very rapidly with increasing number of compartments. Most of the program development work has been done with simulated data, with and without random noise. Some stimulating experience was gained in attempts to deal with uptake and excretion of zinc by the American lobster, Homarus americanus (Waiwood et al 1986).

Table 1. Multicompartment model (MCM) programs

PROGRAM	PURPOSE	INPUT	OUTPUT
MCMSM	Simulation	Rate constants, compartment volumes, initials	Concentrations at various times
MCMRAT	Fitting (least squares)	Concentrations, rates	System parameters or rate constants
MCMSX	Fitting (simplex)	Concentrations; from file only	Rate consts., calcd. concns., to file only
MCMUTL	Utility to edit files	Data or files	Data or files
MCMPLT	Utility	Data or files	Graphics on the HP 2647A terminal

Since the experimental results are usually concentrations, the programs require, in contrast to TCM (Zitko 1982), input of concentrations in compartments and compartment volumes. It is advisable to smoothen experimental data either visually or by some interpolation, polynomial or spline, and to use the interpolated data as input to MCMRAT or MCMSX. MCMRAT requires, in addition to concentrations, their derivatives. These may be obtained readily from spline programs. For example, the IMSL Library (IMSL 1982) provides a variety of spline subroutines that may be used with only minimum additional programming.

A PRIMER ON COMPARTMENTAL ANALYSIS

A compartment is a kinetically homogeneous, distinct amount of a chemical (Jacquez 1972). It may be associated with a tissue or an organ (i.e. gills may be considered a compartment), but an organ may contain several compartments ('bound' and 'free' zinc in the gills). A model consists of one or several compartments. The chemical is transported between compartments at rates characterised by rate coefficients kij, whose dimension is 1/time in a linear model; i=originating, j=destination compartment. The model is 'open' when the chemical is also exchanged with the environment (compartment 0, Fig.1). In nonlinear models, at least one of the rate coefficients is a function of concentration and has a dimension of 1/(time*concentration). Differential equations describing the model are derived from material balances of the chemical in individual compartments (change=input-output).

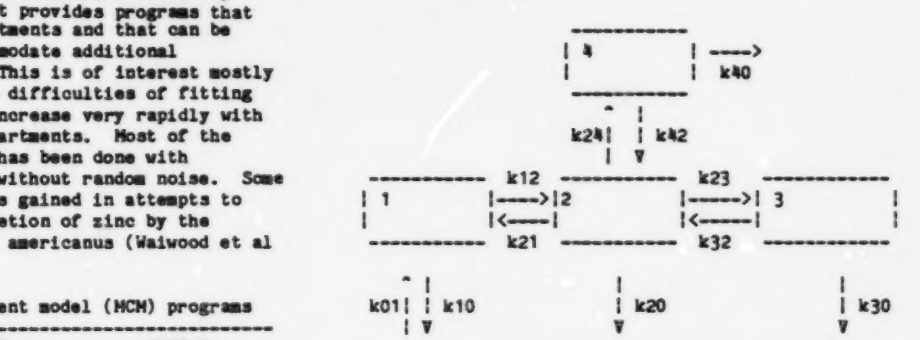

Fig.1 A four compartment mammillary (peripheral compartments 1,3,4 connected to the central compartment 2) open (a chemical enters from, and may be excreted to the environment (compartment 0)) model. The compartments 1-4 may be,for example, gills, blood, liver, and kidney, respectively.

A mass balance for compartment 1 (Fig.1) is:

Input = $k01 \cdot cw + k21 \cdot c2 \cdot V2$ (unit: mass/time)
Output= $k10 \cdot c1 \cdot V1 + k12 \cdot c1 \cdot V1$ (unit: mass/time)

Change = $V1 \cdot dc1/dt = k01 \cdot cw + k21 \cdot c2 \cdot V2 - k10 \cdot c1 \cdot V1 - k12 \cdot c1 \cdot V1$

or

$$dc1/dt = -(k10+k12) \cdot c1 + k21 \cdot V2/V1 \cdot c2 + k01/V1 \cdot cw,$$

where kij= transfer rate coefficients (unit 1/time, except for k01 which is volume/time)
cw = concentration in water
ci = concentration in compartment i (unit mass/volume)
Vi = volume of compartment i (unit volume)

Differential equations for the other compartments may be derived in the same way. The model is then described by a system of differential equations:

$$dc1/dt = -(k10+k12) \cdot c1 + k21 \cdot V2/V1 \cdot c2 + k01/V1 \cdot cw,$$
$$dc2/dt = k12 \cdot V1/V2 \cdot c1 - (k21+k23+k24+k20) \cdot c2 + k32 \cdot V3/V2 \cdot c3 + k42 \cdot V4/V2 \cdot c4$$
$$dc3/dt = k23 \cdot V2/V3 \cdot c2 - (k32+k30) \cdot c3$$
$$dc4/dt = k24 \cdot V2/V4 \cdot c2 - (k42+k40) \cdot c4$$

Matrix notation simplifies matters considerably:

$$[dc/dt] = [c'] = [k] * [c] \qquad (1)$$
(5,1) (5,1) (5,5) (5,1)

where [] indicate matrices with r rows and c columns (r,c), and

$$[k]=\begin{bmatrix} -(k10+k12) & V2/V1*k20 & 0 & 0 & k01/V1 \\ V1/V2*k12 & -(k21+k23+k24+k20) & V3/V2*k32 & V4/V2*k42 & 0 \\ 0 & V2/V3*k23 & -(k32+k30) & 0 & 0 \\ 0 & V2/V4*k24 & 0 & -(k42+k40) & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The structure of the matrix [k] reflects the arrangement of the compartments. The concentration in water, cw becomes c5 in the matrix notation. If it decreased exponentially during the experiment, which is frequently the case, the '0' in the lower right corner of [k] would be replaced by rate coefficient of the decrease. Analytical solution of such a system is very cumbersome, but straightforward, for example by Laplace transformation, but the process is quite unwieldy. Since the fitting of models to data means the estimation of the values of the rate coefficients, only a numerical solution is needed. This is much easier to find, for example by the eigenvalue method or by other numerical methods for solving differential equations. The rate constants may be also estimated from the differential equations by least squares regression. The seeming simplicity of this approach is offset by the need to estimate the derivatives of the concentrations. MCMRAT uses the latter approach, MCMSX solves the differential equations by the 4th order Runge-Kutta method, and MCMSM uses the eigenvalue technique. The Runge-Kutta method provides solution at predetermined points which is all that is needed in the search for best fit, and requires much less code than the eigenvalue method. On the other hand, the eigenvalue method provides a closed numerical solution which is convenient in simulations.

The model structure and the mathematical techniques are routine. The objective of this work was to provide convenient software, working on the equipment available to us (HP 3000).

MCMSM

This program (MultiCompartment Model SiMulation) calculates the concentration of a chemical in up to 9 compartments. The part of the program that calculates eigenvalues and eigenvectors, and the particular solution was put together and tranalated from a Tektronix Mathematics package (1979). Required input includes rate constants, compartment volumes, and initial conditions. These may be supplied manually or from a file. A typical interactive run is illustrated below. See Fig.1 for the arrangement of the compartments. Compartment #1 is always the entrance, and #2 the central compartment. The "Dual hepato" option attaches compartment #5 to compartment #3.

```
**************************************************
MCMSM

Central compartment model (C), other (D) C
Full printout? Y/N Y
Explanation ? Y/N N
Constants manually? Y/N Y
Dual hepato? Y/N N
Number of compartments (water does not count) 3
Excretion? Y/N N
k01             ?150
k10             ?.2
k12             ?18
k21             ?6
k20             ?0
k23             ?1.3
k32             ?.1
k30             ?.5
Volume of compartment  1    ?1
Volume of compartment  2    ?5
Volume of compartment  3    ?8
Exponential decrease in Cw? Y/N N
k01              150
k10              .2
k12              18
k21              6
k20              0
k23              1.3
k32              .1
k30              .5
---------------
VOLUMES
 1     5     8
DIFEQ MATRIX
-18.2          30      0          150
 3.6          -7.3     .16          0
 0            .8125   -.6           0
 0             0       0            0


ALL EIGENVALUES WERE FOUND.
AN EIGENVECTOR WAS FOUND FOR ALL KNOWN EIGENVALUES.
EIGENVECTOR MATRIX
 .978721        -.715152        -.319177         .759768

-.205079        -.405748        -.18901          .386141

 6.97587E-03     .569145        -.928656         .522899

 0               0               0               .014957

LARGEST ELEMENT OF EIGENVECTOR MATRIX  .978721
LARGEST ELEMENT OF INVERTED MATRIX  66.8584
CONDITION FACTOR  65.4357
INPUT INITIAL CONCENTRATIONS
?111
??90
??104
??25
CONSTANTS

-148.167        823.059         1332.48         1671.46

FOR INITIAL CONCENTRATIONS
 111             90              104              25

THE SOLUTION IS
Y(1)=-145.014*EXP(-24.4861*X)+
-588.612*EXP(-1.17924*X)+
-425.295*EXP(-.434631*X)+
 1269.92*EXP(0*X)+
-----------------
Y(2)= 30.3859*EXP(-24.4861*X)+
-333.954*EXP(-1.17924*X)+
-251.851*EXP(-.434631*X)+
 645.419*EXP(0*X)+
```

```
-----------------
Y(3)=-1.03359*EXP(-24.4861*X)+
 468.44*EXP(-1.17924*X)+
-1237.41*EXP(-.434631*X)+
 874.005*EXP(0*X)+
-----------------
Y(4)= 0*EXP(-24.4861*X)+
 0*EXP(-1.17924*X)+
 0*EXP(-.434631*X)+
 25*EXP(0*X)+
-----------------
Print to file as well? Y/N N
Time ---->? 5
STEP .5
```

Time	Concentration in compartments		
0	111	90	104
.5	601.288	257.57	138.058
1	813.536	379.65	216.828
1.5	947.956	457.249	309.158
2	1035.95	508.248	399.505
2.5	1095.57	542.94	481.106
3	1137.35	567.337	551.704
3.5	1167.53	585.017	611.25
4	1189.9	598.162	660.682
4.5	1206.85	608.14	701.302
5	1219.9	615.835	734.454

```
-----------------------------------------------------
New initials(1),Print(2),Constants(3),Range(4),
End(5) 5
=====================================================
```

The "dual hepato" option was developed for the simulation of the behaviour of trace metals in the American lobster. It assumes that the hepatopancreas consists of two compartments. The option can be used only with a 4-compartment model. An example is presented below (see Fig.1 for the arrangement of the compartments 1-4). Hepatopancreas is compartment #3 (and #5 for "dual").

```
=====================================================
MCKSH
Central compartment model (C), other (D) C
Full printout? Y/N Y
Explanation ? Y/N N
Constants manually? Y/N Y
Dual hepato? Y/N Y
Excretion? Y/N N
k01             ?150
k10             ?.2
k12             ?18
k21             ?6
k20             ?0
k23             ?1.3
k32             ?.5
k30             ?.1
k24             ?.5
k42             ?.2
k40             ?0
k35             ?.1
k53             ?.02
k50             ?0
Volume of compartment  1    ?1
Volume of compartment  2    ?5
Volume of compartment  3    ?8
Volume of compartment  4    ?3
Volume of compartment  5    ?2
Exponential decrease in Cw? Y/N N
VOLUMES
 1    5    8    3    2

DIFEQ MATRIX
-18.2        30    0     0     0     150
 3.6       -7.8   .8    .12   0     0
 0      .8125     -.7   0     .005  0
 0      .833333    0    -.2   0     0
 0      0          .4   0     -.02  0
 0      0          0    0     0     0

ALL EIGENVALUES WERE FOUND.
AN EIGENVECTOR WAS FOUND FOR ALL KNOWN EIGENVALUES.
LARGEST ELEMENT OF EIGENVECTOR MATRIX  .997089
LARGEST ELEMENT OF INVERTED MATRIX  3242.06
CONDITION FACTOR  3232.63
INPUT INITIAL CONCENTRATIONS
?111
?790
??104
??104
?280
?725

THE SOLUTION IS
Y(1)=-140.879*EXP(-24.6293*X)+
-391.765*EXP(-1.83498*X)+
-276.006*EXP(-.372333*X)+
-1613.71*EXP(-7.33783E-02*X)+
-1999.18*EXP(-9.99719E-03*X)+
 4532.54*EXP(0*X)+
-----------------
Y(2)= 30.1919*EXP(-24.6293*X)+
-213.708*EXP(-1.83498*X)+
-164.018*EXP(-.372333*X)+
-975.037*EXP(-7.33783E-02*X)+
-1212.17*EXP(-9.99719E-03*X)+
 2624.74*EXP(0*X)+
-----------------
Y(3)=-1.02514*EXP(-24.6293*X)+
 153.137*EXP(-1.83498*X)+
-399.781*EXP(-.372333*X)+
-1192.94*EXP(-7.33783E-02*X)+
-2009.73*EXP(-9.99719E-03*X)+
 3554.34*EXP(0*X)+
-----------------
Y(4)=-1.02991*EXP(-24.6293*X)+
 108.925*EXP(-1.83498*X)+
 793.123*EXP(-.372333*X)+
-6416.98*EXP(-7.33783E-02*X)+
-5316.47*EXP(-9.99719E-03*X)+
 10936.4*EXP(0*X)+
-----------------
Y(5)= 1.66627E-02*EXP(-24.6293*X)+
-33.7496*EXP(-1.83498*X)+
 453.87*EXP(-.372333*X)+
 8939.51*EXP(-7.33783E-02*X)+
-80366.4*EXP(-9.99719E-03*X)+
 71086.7*EXP(0*X)+
-----------------
Y(6)= 0*EXP(-24.6293*X)+
 0*EXP(-1.83498*X)+
 0*EXP(-.372333*X)+
 0*EXP(-7.33783E-02*X)+
 0*EXP(-9.99719E-03*X)+
 25*EXP(0*X)+
-----------------
Print to file as well? Y/N
N
Time ---->? 5
STEP 1
```

```
Time                Concentration in compartments
-------------------------------------------------------------
 0     110.998    89.9995   104       103.998    80
 1     800.971    371.436   205.006   273.816    134.203
 2     1038.43    511.283   368.333   563.537    245.25
 3     1205.65    611.46    516.551   887.988    416.422
 4     1345.98    695.934   643.826   1222.55    638.688
 5     1469.78    770.572   753.912   1556.22    903.375
-------------------------------------------------------------
Concentration in combined hepatopancreas compartment
 99.2          NOTE: HEPATOPANCREAS CONSISTS OF
 190.846       COMPARTMENT 3 WITH VOLUME 8 AND
 343.716       COMPARTMENT 5 WITH VOLUME 2.
 496.525       FOR EXAMPLE AT TIME 0, CONCENTRATION
 642.798       IN COMBINED HEPATOPANCREAS IS:
 783.804       (104*8+80*2)/(8+2) = 99.2

New initials(1),Print(2),Constants(3),Range(4),
End(5),3
 1    k01       150
 2    k10       .2
 3    k12       18
 4    k21       6
 5    k20       0
 6    k23       1.3
 7    k32       .5
 8    k30       .1
 9    k24       .5
 10   k42       .2
 11   k40       0
 12   k35       .1
 13   k53       .02
 14   k50       0
Change constant number (0 if done )13
?.05
Change constant number (0 if done )0
Exponential decrease in Cw? Y/N N
DIFEQ MATRIX
-18.2     30        0      0      0      150
 3.6     -7.8       .8     .12    0      0
 0        .8125     -.7    0      .0125  0
 0        .833333    0     -.2    0      0
 0        0          .4    0     -.05    0
 0        0          0     0      0      0

ALL EIGENVALUES WERE FOUND.
AN EIGENVECTOR WAS FOUND FOR ALL KNOWN EIGENVALUES.
LARGEST ELEMENT OF EIGENVECTOR MATRIX  .977748
LARGEST ELEMENT OF INVERTED MATRIX  1477.67
CONDITION FACTOR  1444.79

THE SOLUTION IS
Y(1)=-140.88*EXP(-24.6293*X)+
-391.208*EXP(-1.83542*X)+
-277.033*EXP(-.377665*X)+
-941.865*EXP(-8.67701E-02*X)+
-2670.56*EXP(-2.08321E-02*X)+
 4532.55*EXP(0*X)+
-----------------
Y(2)= 30.192*EXP(-24.6293*X)+
-213.399*EXP(-1.83542*X)+
-164.579*EXP(-.377665*X)+
-568.674*EXP(-8.67701E-02*X)+
-1618.29*EXP(-2.08321E-02*X)+
 2624.75*EXP(0*X)+
-----------------
Y(3)=-1.02515*EXP(-24.6293*X)+
 153.085*EXP(-1.83542*X)+
-396.097*EXP(-.377665*X)+
-616.713*EXP(-8.67701E-02*X)+
-2589.59*EXP(-2.08321E-02*X)+
 3554.34*EXP(0*X)+
-----------------
Y(4)=-1.02991*EXP(-24.6293*X)+
 108.738*EXP(-1.83542*X)+
 771.955*EXP(-.377665*X)+
-4185.24*EXP(-8.67701E-02*X)+
-7526.86*EXP(-2.08321E-02*X)+
 10936.4*EXP(0*X)+
-----------------
Y(5)= 1.66832E-02*EXP(-24.6293*X)+
-34.2966*EXP(-1.83542*X)+
 483.539*EXP(-.377665*X)+
 6708.85*EXP(-8.67701E-02*X)+
-35512.9*EXP(-2.08321E-02*X)+
 28434.8*EXP(0*X)+
-----------------
Y(6)= 0*EXP(-24.6293*X)+
 0*EXP(-1.83542*X)+
 0*EXP(-.377665*X)+
 0*EXP(-8.67701E-02*X)+
 0*EXP(-2.08321E-02*X)+
 25*EXP(0*X)+
-----------------
Print to file as well? Y/N N
Time                Concentration in compartments
-------------------------------------------------------------
 0  110.999   89.999   104.      103.996   79.9961
 1  801.148   371.553  205.597   273.85    131.281
 2  1039.03   511.663  369.754   563.744   237.441
 3  1206.96   612.288  519.318   888.608   400.234
 4  1348.43   697.462  648.584   1223.93   609.375
 5  1473.86   773.106  761.352   1558.88   855.359
-------------------------------------------------------------
Difference, new-old
-------------------------------------------------------------
  .0     .00   - .00   -  .00   -  .00   -   .00
 1.0     .18     .12     .59      .03   -  2.92
 2.0     .60     .38    1.42      .21   -  7.81
 3.0    1.31     .83    2.77      .62   - 16.19
 4.0    2.45    1.53    4.76     1.38   - 29.31
 5.0    4.07    2.53    7.44     2.66   - 48.02
-------------------------------------------------------------
Concentration in combined hepatopancreas compartment
 99.1988
 190.734
 343.292
 495.502
 640.743
 780.153
New initials(1),Print(2),Constants(3),Range(4),
End(5) 5
=============================================================
```

MCMSM allows us to study the effects of changes of the rate coefficients. This was illustrated in the second part of the example above, when the rate coefficient k53 was changed from .02 to .05.

The "condition factor" in the example refers to the eigenvector matrix. The higher the value, the poorer the condition of the matrix and stability of the solution. Low values of the excretion rate coefficients result in ill-conditioned systems (see the above example for the effect of the change in k53 on the condition factor). Visually, if the compartmental concentrations vs time curves approach straight lines (a sign of an ill-conditioned system), there is not much point in attempting compartmental analysis.

"Stiffness" of the system is another factor

seriously affecting attempts to estimate the rate coefficients. This term refers to the behaviour of the system with time. Compartmental concentrations are sums of exponential terms. If some of the terms disappear with time much faster than others, the system is "stiff" and causes problems during the numerical integration of its differential equations. Attempts to estimate the rate coefficients suffer as well.

In the first example above, the value of the term "-145.014*EXP(-27.4861*X) is -145, -9.3, -.59, -.0038, and -.0024, for X=0, .1, .2, .3, and .4. Supposing for example that X is in days and the first measurement was done at 0.5 day of exposure, the rate coefficients of the 3-compartment model could be determined only from extremely accurate data. The first term has an effect only at times below 0.5 day. The model "degenerates" into a hypothetical one with one less compartment. This situation will be discussed further in connection with the program MCMRAT.

MCMRAT

This program calculates the differential equations matrix for a system of up to 10 compartments and, optionally, rate constants of a mammillary system consisting of up to 5 compartments. The former is calculated by the least squares technique from the differential equations of the system. The number of experimental points must be at least equal to the number of compartments. In such a case there may be a single solution or no solution. Hopefully, the number of points will be always considerably larger than the number of compartments, in which case there is a best ("least worst",copyright Dr.D.Mackay) solution.

Unfortunately, the solution may be meaningless even with moderately noisy data. The outcome of the calculations is very sensitive to the accuracy of the rates. These are very difficult to determine accurately even under the best of circumstances. If the concentrations in compartments and their derivatives are known at 'm' times, the equation (1) becomes

$$[C']_{(5,m)} = [k]_{(5,5)} * [C]_{(5,m)} \qquad (2)$$

where [C'] = matrix of derivatives;
rows=compartments;
columns=times
[k] = system matrix as in (1)
[C] = matrix of concentrations;
rows=comparments;
columns=times.

The equation (1) is valid for each individual set of derivatives and concentrations, [c']=[k]*[c]. Consequently, these can be combined to form columns of [C'] and [C]. [C'] and [C] are known and the objective is to calculate [k]. This is accomplished by linear regression which, in matrix notation is

$$[k] = [C'] * [C]` * ([C]*[C]`)**(-1) \qquad (3)$$

where []` = transposed matrix (rows and columns exchanged)

Once [k] is known, the rate coefficients kij may be calculated depending on the structure of the model. MCMRAT is used for entering data as well as for the calculations. The program attempts to come up with a mammillary model matrix, but the intermediate matrices may be printed as well. The general structure of [k] for a mammillary model with compartment 2 as the central compartment, and the chemical administered in water, is:

```
 *    *    0    0    0 ........    0    *
 *    *    *    *    *             *    0
 0    *    *    0    0             0    0
 0    *    0    *    0             0    0
 0    *    0    0    *             0    0
 .    .    .    .    .             .    .
 .    .    .    .    .             .    .
 .    .    .    .    .             .    .
 0    *    0    0    0             *    0
 0    0    0    0    0             0    0
```

MCMRAT may be used also to estimate constants of "degenerate" systems. The input is a data file for the full system (for example 3 compartments). It is also possible to use fewer compartments than specified by the data. This may be necessary for degenerate models for which some exponential terms decay to zero without being captured adequately by experimental data. The "degenerate" system calculations can be performed on up to N-1 compartments (in this case 1 and 2).

```
==================================================
MCMRAT
Write file (1), calculate (2), explanation (3) 2
Print intermediate matrices? Y/N N
Filename TRIGGER
THE NUMBER OF COMPARTMENTS IS  3
ANALYZE DEGENERATE MODELS? YES(1),NO(2) 1
NUMBER OF COMPARTMENTS 2
ENTER DESIRED COMPARTMENTS, I.E.  13 12
- 18.20      30.00      150.00
   3.23    -  6.39         .00
    .00         .00         .00
Constants calculation(1),NEW calcn(2),file(3),
end(4) 1
Compartment  1 volume
?1
Compartment  2 volume
?5
k01              149.999
k10              2.06595
k12              16.134
k21              5.99998
k20              .389161
Constants calculation(1),NEW calcn(2),file(3),
end(4) 2
Filename TRIGGER
THE NUMBER OF COMPARTMENTS IS  3
ANALYZE DEGENERATE MODELS? YES(1),NO(2) 1
NUMBER OF COMPARTMENTS 2
ENTER DESIRED COMPARTMENTS,(I.E.  13)13
-  6.12       4.61      173.55
    .35    -   .49         .00
    .00         .00         .00
Constants calculation(1),NEW calcn(2),file(3),
end(4) 1
Compartment  1 volume
?1
Compartment  2 volume
?8
```

```
k01              173.546
k10              3.31686
k12              2.79817
k21              .575912
k20              -8.37641E-02
Constants calculation(1),NEW calcn(2),file(3),
end(4) 4
=====================================================

 MCMSX

     Multicompartment Model SimpleX attempts to find
best fitting values of rate constants.  It requires
an initial estimate of the rate constants, values
for compartment volumes, fitted data, and control
parameters.  The program is best run compiled and as
a "job", rather than from the terminal.  That is why
the data input is in the form of files.  Two
separate files are used to be able to change the
initial constants estimate without having to modify
the rest of the file.

     The control parameters include the number of
iterations (usually about 100), initial simplex span
(10-50 are good for first trial), Runge-Kutta
tolerance which controls the step size in the
integration of the differential equations (0.01 is
the commonly used value), and convergence tolerance
to stop the program when the simplex becomes very
small (0.1 may be used).  The program is stopped
either by the number of iterations specified or by
the convergence tolerance (most often the former).
The output goes to a user-specified file.

     The initial simplex is selected more or less
randomly around the specified set of rate constants.
The "simplex span" value controls the size of the
simplex.  The initial simplex values are printed.
The last row contains the sum of squared deviations
between measured and calculated data.  The data are
scaled relative to the measured values.  This may or
may not be a good idea.  It eliminates the bias
provided  by a compartment containing a high
concentration.  On the other hand, this may be the
compartment that should be fitted most accurately.
To remove the scaling, remove the term d[J,I+1] from
the denominator in the statement 3950.

     The input and output files may be prepared and
read, respectively, by MCMUTL.  An example run is
given below.

=====================================================
Data input file SBR
Constants input file SBRC
Data output file SRPEN
Number of iterations 20
Initial simplex span 10
Runge-Kutta tolerance .01
Convergence tolerance .1
20       45.4762    117.778     1.70912    47.3406
16.3485 75.7084     49.4772     1.64549   117.614
85.3365 20.4065

 .1        .345091     .344133   .385088    4.86013E-02
 .269605   .50228_     .123331   .409429     .607748
 .553572   .888789

 .1        .466615     .494427   .135619    1.03985E-02
 .328351   .258659     .482434   .108934     .499863
 .353403   .685694

 .05       .200608     .245729   .200401    .265232
 .137543   .234901     .218601   .130248   3.07153E-02
 .100869   .243331

 0         0           0         0          0
 0         0           0         0          0
 0         0

 .2        1.09095     .873084   .260023    .108413
 .753078   .4947       .04932   7.51951E-02 .974285
 1.55737   .412416

 .1        .529918     .498984   .116022    .209914
7.91937E-02.394791     .311972   .803602    .112343
 .211925   6.19228E-02

 .02       7.3083E-02 9.5378E-02 9.739E-02 6.1301E-02
3.649E-02 9.9 693E-03 .013131   1.631E-02 3.5057E-02
3.3335E-02 .111172

 .001      5.4238E-03 7.0770E-04 3.465E-04 5.1407E-03
8.082E-03 7.5334E-04 7.0902E-03 4.011E-03 1.0266E-03
4.169E-03 1.7264E-03

 .0008     3.1565E-03 3.3765E-03 5.030E-03 2.0059E-03
1.033E-03 4.0248E-03 3.1759E-03 1.670E-03 3.9039E-03
4.300E-03 4.6932E-04

 0          0          0          0          0
 0          0          0          0          0
 0          0

17.1771   10.8266    25.9901     28.6391    22.3129
21.1356   15.2637    10.7281     27.2291    17.9864
15.3818   22.1894

 0  1  2  3  4  5  6  7  9  10 11 12
 14 16 17 19 20
NOT CONVERGED
Time  Concentration ( Data <-> Calculated)
        (I.E.  214 is experimental value,
            345 is calculated value)
-----------------------------------------------
  .1  214  345  118  88    85 106  72  80
  .2  312  543  143  90    96 107  73  80
  .3  408  712  167  95   107 110  74  80
  .4  503  870  191 103   118 112  75  80
  .5  596 1027  215 114   129 117  76  80
  .6  687 1154  240 127   141 122  78  80
  .7  774 1257  264 140   152 128  79  80
  .8  860 1366  288 158   164 138  80  80
 1.0 1026 1484  336 184   188 156  82  80
 1.2 1184 1564  382 208   212 177  84  80
 1.4 1337 1619  427 230   238 200  86  80
 1.6 1484 1659  469 250   265 225  88  80
 1.8 1625 1688  509 269   293 251  90  80
 2.0 1761 1711  546 287   323 277  92  80
 2.5 2082 1743  623 320   403 330  97  80
 3.0 2384 1766  687 351   493 382 103  80
 3.5 2677 1785  742 380   589 434 108  81
 4.0 2965 1803  795 409   689 484 113  81
-----------------------------------------------

Best fit constants
 103.492
 .745221
 .873672
 .172447
 0
 1.34784
 .47063
```

```
5.05017E-02
4.28930E-03
4.92154E-03
0
```

==========

Fitting multicompartmental models is difficult by the mathematical nature of the problem. The sums of exponentials are in a sense very flexible by being able to accommodate all kinds of concentration vs time curves by using quite different parameters. This is extremely confusing to the simplex and attempts to obtain a very good fit may become frustrating.

MCMUTL

This program (MultiCompartment Model UTiLity) is used to manipulate MCM-type files since all of them are BASIC-formatted and not accessible by the general editor programs.

There are 3 types of files: CONSTANTS, DATA, and OUTPUT. Constants files contain intercompartment transfer rate constants and are used in input to MCMSM and to MCMSX (optional). Numbers indicate originating and receiving compartment, respectively. '0' is water, '1' is the entry compartment, and '2' is the central compartment. All compartments are connected to '2' (mammillary model). Maximum number of compartments is 9. It is possible to have one compartment not connected directly to the central compartment. This model, referred to as the 'DUAL HEPATO' model consists of 5 compartments, with the compartment number 5 connected to the compartment number 3. Dual hepato files may be written directly or 4-compartment mammillary model files may be CONVERTED into dual hepato files. Data files contain compartment volumes and concentrations at different times, and are used in input to MCMSM. Output files from both MCMSM and MCMSX contain calculated concentrations and various other parameters as well and may be used in place of data files. Random noise at specified relative level may be ADDED to data files. This is to investigate the effect of 'experimental errors' on 'successful' fit. Real data do not need this option.

As an example of MCMUTL output, this is its output for the files SBR, SBRC, and SRPEN used above in the demonstration of MCMSX:

```
==========
Read(R), Write, convert or add noise(W), End(/) R
File name (input or new file) SBR
Number of compartments  4
UPTAKE
Volumes:
 1.03          5.28          8.48          9.56

Initial concentrations (water last)
 111       90          104         80          25

Rate constant for concentration decrease in water 0
```

Time	Concentration			
	1	2	3	4
.1	214.00	118.00	85.00	72.00
.2	312.00	143.00	96.00	73.00
.3	408.00	167.00	107.00	74.00
.4	503.00	191.00	118.00	75.00
.5	596.00	215.00	129.00	76.00
.6	687.00	240.00	141.00	78.00
.7	774.00	264.00	152.00	79.00
.8	860.00	288.00	164.00	80.00
1.0	1026.00	336.00	188.00	82.00
1.2	1184.00	382.00	212.00	84.00
1.4	1337.00	427.00	238.00	86.00
1.6	1484.00	469.00	265.00	88.00
1.8	1625.00	509.00	293.00	90.00
2.0	1761.00	546.00	323.00	92.00
2.5	2082.00	623.00	403.00	97.00
3.0	2384.00	687.00	493.00	103.00
3.5	2677.00	742.00	589.00	108.00
4.0	2965.00	795.00	689.00	113.00

```
==========
Read(R), Write, convert or add noise(W), End(/) R
File name (input or new file) SBRC
Number of compartments  4
UPTAKE
k01             20
k10             .1
k12             .1
k21             .05
k20             0
k23             .2
k32             .1
k30             .02
k24             .001
k42             .0008
k40             0
Read(R), Write, convert or add noise(W), End(/) R
File name (input or new file) SRPEN
Number of compartments  4
UPTAKE
Volumes:
 1.03          5.28          8.48          9.56

Initial concentrations (water last)
 111       90          104         80          25

Rate constant for concentration decrease in water 0
```

Time	Concentration			
	1	2	3	4
.1	214.00	118.00	85.00	72.00
.2	312.00	143.00	96.00	73.00
.3	408.00	167.00	107.00	74.00
.4	503.00	191.00	118.00	75.00
.5	596.00	215.00	129.00	76.00
.6	687.00	240.00	141.00	78.00
.7	774.00	264.00	152.00	79.00
.8	860.00	288.00	164.00	80.00
1.0	1026.00	336.00	188.00	82.00
1.2	1184.00	382.00	212.00	84.00
1.4	1337.00	427.00	238.00	86.00
1.6	1484.00	469.00	265.00	88.00
1.8	1625.00	509.00	293.00	90.00
2.0	1761.00	546.00	323.00	92.00
2.5	2082.00	623.00	403.00	97.00
3.0	2384.00	687.00	493.00	103.00
3.5	2677.00	742.00	589.00	108.00
4.0	2965.00	795.00	689.00	113.00

==========

```
k01              103.492
k10              .745221
k12              .873672
k21              .172447
k20              0
k23              1.34784
k32              .47063
k30              5.05017E-02
k24              4.28930E-03
k42              4.92154E-03
k40              0
Number of iterations          21
Simplex status
 91.0878 45.4762   53.8969   94.5619   56.4282
 103.492 64.7455   49.4772  103.176    60.1373
 73.7273 54.9485

 .799732   .345091   .6755     .592364   .775278
 .745221   .510284   .123331   .611776   .630482
 .522419   .572549


 .718855   .466615   .749219   .665887   .727998
 .873672   .82858    .482434   .763676   .873271
 .417384   .524414

 .273954   .200608   .114669   .155548  5.45452E-02
 .172447   .103789   .218601   .195534   .234975
 .137968   .183522

 0         0         0         0         0
 0         0         0         0         0
 0         0

1.25105   1.09095   1.24654   1.17092   1.17219
1.34784   1.36468    .04932   1.32388   1.34435
1.16122    .734396

 .5267     .529918   .26944    .475909   .319264
 .4706     .268247   .311972   .164192   .498379
 .28911    .259391

 .06901   7.208E-02 2.2633E-02 .016918 3.10317E-02
5.050E-02 8.1087E-02 .01311   5.27E-02 5.31255E-02
3.805E-02 5.8087E-02

5.729E-03 5.424E-03 7.259E-03 5.46E-03 1.60274E-03
4.289E-03 7.679E-03 7.090E-03 4.02E-03 8.00515E-03
3.997E-03 3.266E-03

5.421E-03 3.156E-03 3.665E-03 2.73E-03 3.42083E-03
4.921E-03 2.695E-03 3.176E-03 4.31E-03 3.84959E-03
3.708E-03 2.607E-03

0         0         0         0         0
0         0         0         0         0
0         0

9.98522  10.8266   10.99     10.0625   10.6341
8.98247   9.91375  10.7281   12.0137    9.9301
11.9773  11.2192

Time      Concentration ( Data <-> Calculated)
       (i.e.  214 = experiment;345 = calculation)
-------------------------------------------------
  .1  214   345  118  88   85 106  72   79
  .2  312   543  143  90   96 107  73   79
  .3  408   712  167  95  107 110  74   79
  .4  503   870  191 103  118 112  75   79
  .5  596  1027  215 114  129 117  76   79
  .6  687  1154  240 127  141 122  78   79
  .7  774  1257  264 140  152 128  79   79
  .8  860  1366  288 158  164 138  80   79
 1.0 1026  1484  336 184  188 156  82   79
 1.2 1184  1564  382 208  212 177  84   79
 1.4 1337  1619  427 230  238 200  86   79
 1.6 1484  1659  469 250  265 225  88   79
 1.8 1625  1688  509 269  293 251  90   80
 2.0 1761  1711  546 287  323 277  92   81
 2.5 2082  1743  623 320  403 330  97   81
 3.0 2384  1766  687 351  493 382 103   81
 3.5 2677  1785  742 380  589 434 108   81
 4.0 2965  1803  795 409  689 484 113   81
-------------------------------------------------
Read(R), Write, convert or add noise(W), End(/) /
=================================================
```

MCMPLT9

MultiCompartment Model PLoTter, with "9" indicating that this is a program in HP Terminal BASIC) displays graphically the results. Since one usually works with the same data for a while, the best thing is to have the data incorporated in the program. One can then input parameters of the equations (coefficient and exponents) and plot the curves. An example from the data of Waiwood et al (1986) is given below (Fig.2). The graph contains the means and standard deviations of the original data, cubic spline "smoothened" points ("x") and a continuous curve obtained by the model.

ACKNOWLEDGMENTS

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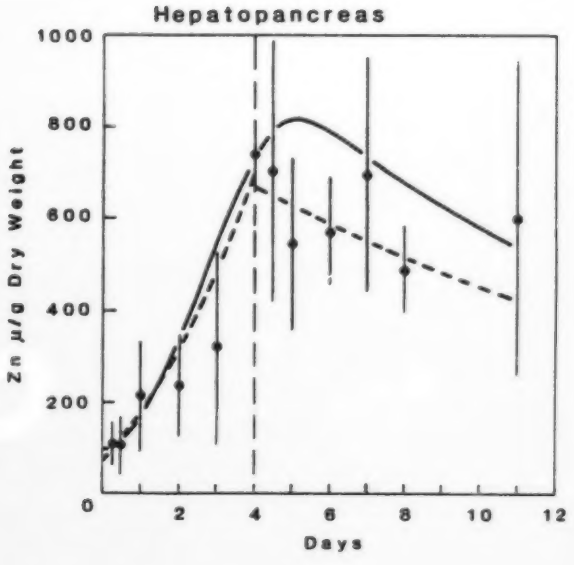

Fig. 2. Uptake and excretion of cadmium by lobster hepatopancreas (Waiwood et al., 1986).

An example of MCMLPT9 output.

APPENDIX

APPENDIX

```
*******************************************************
 >>>>>>>>>>MCMSM<<<<<<<<<<<<<
 10 DIM A[10,10],E3[10,10],E1[10],E0[10],E2[10,10]
 20 DIM N1$[10],N2$[10]
 30 DIM F[10,10],Y[10,10],Z3[10],F1[10]
 40 DIM D[30,10],Y4[10],Y5[50]
 50 DIM Q[20,5]
 60 DIM W[30,10],W1[30,10]
 70 DIM T[30]
 80 DIM K$[26,3],X[26],V[10]
 90 Z9=Z8=0
100 Z5=Z6=Z7=0
110 FILES *,*
120 GOTO 410
130 REM  ************************************************************
140 REM  REFN: BURTON S. GARBOW, ARGONNE NATIONAL LABORATORY,
150 REM        ARGONNE, ILLINOIS, MAY 1969.  ANL F265S EIGENP
160 REM  REFN: ALGORITHM 343, COMMUNICATIONS OF THE ACM,
170 REM        DECEMBER 1968, J. GRAD AND M.A. BREBNER.
180 REM  VARIABLES:  N AND A ARE USED ALONG WITH ANY VARIABLE
190 REM        NAME STARTING WITH E,P,Q, OR R.
200 REM  PARAMETERS
210 REM    ***INPUT***
220 REM    A - THE MATRIX WHOSE EIGENVALUES (AND EIGENVECTORS,
230 REM        IF DESIRED) ARE FOUND.  IT IS DESTROYED BY THE
240 REM        ROUTINE.
250 REM    N - THE # OF ROW (=#COLUMNS) OF A.
260 REM    ***OUTPUT***
270 REM    E0,E1 - LINEAR ARRAYS OF LENGTH N IN WHICH THE REAL(E0)
280 REM        AND IMAGINARY(E1) PARTS OF THE EIGENVALUES OF
290 REM        A ARE STORED.
300 REM    E2,E3 - N BY N ARRAYS IN WHICH THE REAL(E2) AND
310 REM        IMAGINARY(E3)  PARTS OF THE NORMALIZED EIGENVECTORS
320 REM        OF A ARE STORED.  THE J'TH EIGENVECTOR IS IN THE
330 REM        J'TH COLUMNS OF E2 AND E3.
340 REM            A REAL EIGENVECTOR IS NORMALIZED SO THAT THE SUM
350 REM        OF THE SQUARES OF THE COMPONENTS IS EQUAL TO ONE.
360 REM        A COMPLEX EIGENVECTOR IS NORMALIZED SO THAT THE
370 REM        LARGEST COMPONENT (IN ABSOLUTE VALUE)  HAS REAL
380 REM        PART EQUAL TO ONE AND IMAGINARY PART ZERO.
390 REM  ************************************************************
400 REM  ********** DATA ENTRY ROUTINE **********
410 MAT A=ZER
420 INPUT "Central compartment model (C), other (D) ",Q1$
430 INPUT "Full printout? Y/N ",Q4$
440 IF Q1$="D" THEN 470
450 IF Q1$="C" THEN GOSUB 7840
460 GOTO 600
470 INPUT "Number of columns (=rows) in diff.eq. matrix ",N
475 INPUT "Excretion? Y/N ",Q2$
480 N1=N-1
485 IF Q2$="Y" THEN N1=N
490 N9=5+(N1-2)*3
500 PRINT "ENTER THE MATRIX"
```

```
510 REDIM A[N,N],Z3[N],F1[N],F[N,N],Y[N,N]
520 FOR P1=1 TO N
530   PRINT
540   PRINT "ROW ";P1
550   FOR P2=1 TO N
560     PRINT "A(";P1;",";P2;")  =  ";
570     INPUT A[P1,P2]
580   NEXT P2
590 NEXT P1
600 REM  **************SCALE A BEFORE FINDING EIGENVALUES***********
610 REDIM E0[N],E1[N],E3[N,N],P[N,3]
620 IF N>1 THEN 700
630 REDIM E2[1,1],Q[1,5]
640 E0[1]=A[1,1]
650 E1[1]=0
660 E2[1,1]=1
670 E3[1,1]=0
680 P[1,1]=2
690 P1=1
700 GOSUB 730
710 GOTO 1310
720 REM  ********** SCALE A **********
730 FOR P1=1 TO N
740   FOR P2=1 TO N
750     E3[P1,P2]=A[P1,P2]
760   NEXT P2
770   P[P1,2]=1
780 NEXT P1
790 Q1=.75
800 Q2=1.33
810 P3=0
820 P4=0
830 FOR P1=1 TO N
840   Q7=0
850   Q8=0
860   FOR P2=1 TO N
870     IF P1=P2 THEN 900
880     Q7=Q7+ABS(A[P2,P1])
890     Q8=Q8+ABS(A[P1,P2])
900   NEXT P2
910   IF Q7*Q8=0 THEN 950
920   Q3=Q7/Q8
930   IF Q3<Q1 THEN 970
940   IF Q3>Q2 THEN 970
950   P4=P4+1
960   GOTO 1040
970   Q9=SQR(Q3)
980   FOR P2=1 TO N
990     IF P1=P2 THEN 1020
1000    A[P1,P2]=A[P1,P2]*Q9
1010    A[P2,P1]=A[P2,P1]/Q9
1020  NEXT P2
1030  P[P1,2]=P[P1,2]*Q9
1040 NEXT P1
1050 P3=P3+1
1060 IF P3>30 THEN 1220
1070 IF P4<N THEN 820
```

```
1080 Q4=0
1090 FOR P1=1 TO N
1100   FOR P2=1 TO N
1110     Q3=A[P1,P2]
1120     Q4=Q4+Q3*Q3
1130   NEXT P2
1140 NEXT P1
1150 Q4=SQR(Q4)
1160 FOR P1=1 TO N
1170   FOR P2=1 TO N
1180     A[P1,P2]=A[P1,P2]/Q4
1190   NEXT P2
1200 NEXT P1
1210 RETURN
1220 FOR P1=1 TO N
1230   P[P1,2]=1
1240   FOR P2=1 TO N
1250     A[P1,P2]=E3[P1,P2]
1260   NEXT P2
1270 NEXT P1
1280 Q4=1
1290 RETURN
1300 REM  ********** END OF SCALING ***********
1310 REM ***PDIFEQ5*****************************************************
1320 REM  ****************** FIND EIGENVALUES ********************
1330 E8=48
1340 Q6=1/2**E8
1350 GOSUB 1740
1360 REM  ************ OUTPUT EIGENVALUES **************
1370 PRINT
1380 GOTO 1410
1390 PRINT " EIGENVALUES"
1400 PRINT "  #    REAL PART              IMAGINARY PART"
1410 FOR P1=1 TO N
1420   REM PRINT P1," ";
1430   IF P[P1,1]<>0 THEN 1470
1440   PRINT "  NOT FOUND"
1450   GOTO 1470
1460   PRINT E0[P1]*Q4,E1[P1]*Q4
1470 NEXT P1
1480 V9=0
1490 FOR P1=1 TO N
1500   IF E1[P1]=0 THEN 1520
1510   V9=1
1520 NEXT P1
1530 IF V9=1 THEN PRINT "COMPLEX EIGENVALUE(S)"
1540 IF V9=1 THEN END
1550 REM  ********** END OF EIGENVALUE OUTPUT ***********
1560 P2=N
1570 P1=1
1580 REDIM E2[N,N],Q[N,5]
1590 Q=0
1600 Q[1,5]=1
1610 IF P2=1 THEN 1680
1620 IF ABS(P[P2-1,3])>Q5 THEN 1650
1630 P1=P1+1
1640 Q[P1,5]=0
```

```
1650 P2=P2-1
1660 Q[P1,5]=Q[P1,5]+1
1670 IF P2<>1 THEN 1620
1680 P3=1
1690 P8=0
1700 P4=Q[1,5]
1710 P5=N
1720 GOTO 3770
1730 REM  ********* FIND EIGENVALUES *********
1740 IF N<2 THEN 2320
1750 IF N>2 THEN 1780
1760 P[1,3]=A[2,1]
1770 GOTO 2320
1780 P5=N-2
1790 FOR P3=1 TO P5
1800   P4=P3+1
1810   Q1=0
1820   FOR P1=P4 TO N
1830     E3[P1,P3]=A[P1,P3]
1840     Q1=Q1+ABS(A[P1,P3])
1850   NEXT P1
1860   IF Q1<>ABS(A[P4,P3]) THEN 1910
1870   P[P3,3]=A[P4,P3]
1880   E3[P4,P3]=0
1890   GOTO 2270
1900   REM  **************
1910   Q3=0
1920   FOR P1=P4 TO N
1930     Q2=A[P1,P3]/Q1
1940     A[P1,P3]=Q2
1950     Q3=Q3+Q2*Q2
1960   NEXT P1
1970   Q2=SQR(Q3)
1980   IF A[P4,P3]<0 THEN 2000
1990   Q2=-Q2
2000   Q3=Q3-Q2*A[P4,P3]
2010   A[P4,P3]=A[P4,P3]-Q2
2020   P[P3,3]=Q2*Q1
2030   E3[P4,P3]=E3[P4,P3]-P[P3,3]
2040   Q7=Q1*SQR(Q3)
2050   FOR P1=P4 TO N
2060     E3[P1,P3]=E3[P1,P3]/Q7
2070     P[P1,3]=A[P1,P3]/Q3
2080   NEXT P1
2090   FOR P2=P4 TO N
2100     Q2=0
2110     FOR P1=P4 TO N
2120       Q2=Q2+A[P1,P3]*A[P1,P2]
2130     NEXT P1
2140     FOR P1=P4 TO N
2150       A[P1,P2]=A[P1,P2]-P[P1,3]*Q2
2160     NEXT P1
2170   NEXT P2
2180   FOR P2=1 TO N
2190     Q2=0
2200     FOR P1=P4 TO N
2210       Q2=Q2+A[P2,P1]*A[P1,P3]
```

```
2220      NEXT P1
2230      FOR P1=P4 TO N
2240        A[P2,P1]=A[P2,P1]-P[P1,3]*Q2
2250      NEXT P1
2260    NEXT P2
2270 NEXT P3
2280 FOR P3=1 TO P5
2290   A[P3+1,P3]=P[P3,3]
2300 NEXT P3
2310 P[N-1,3]=A[N,N-1]
2320 Q5=0
2330 FOR P3=1 TO N
2340   P[P3,1]=0
2350   IF P3=N THEN 2370
2360   Q5=Q5+P[P3,3]**2
2370   FOR P1=P3 TO N
2380     E3[P3,P1]=A[P3,P1]
2390     Q5=Q5+A[P3,P1]**2
2400   NEXT P1
2410 NEXT P3
2420 Q5=Q6*SQR(Q5)
2430 REM  ***** QR ITERATION *****
2440 R2=A[N,N-1]
2450 IF N<=2 THEN 2500
2460 IF A[N,N]<>0 THEN 2500
2470 IF A[N-1,N]<>0 THEN 2500
2480 IF A[N-1,N-1]<>0 THEN 2500
2490 GOTO 2510
2500 R2=0
2510 P5=N
2520 P8=0
2530 P6=10*N
2540 FOR P1=1 TO N-1
2550   FOR P3=1 TO N
2560     IF A[P1,P3]<>0 THEN 2650
2570   NEXT P3
2580 NEXT P1
2590 FOR P1=1 TO N
2600   P[P1,1]=1
2610   E0[P1]=A[P1,P1]
2620   E1[P1]=0
2630 NEXT P1
2640 RETURN
2650 P3=P5-1
2660 P7=P3
2670 P1=P3
2680 IF P3<0 THEN 2640
2690 IF P3=0 THEN 3480
2700 IF ABS(A[P5,P3])<=Q5 THEN 3480
2710 IF P5=2 THEN 3540
2720 P1=P1-1
2730 IF ABS(A[P3,P1])<=Q5 THEN 2760
2740 P3=P1
2750 IF P3>1 THEN 2720
2760 IF P3=P7 THEN 3540
2770 Q1=A[P5,P5]+A[P7,P7]+R2
2780 Q2=A[P5,P5]*A[P7,P7]-A[P5,P7]*A[P7,P5]+.25*R2*R2
```

```
2790 A[P3+2,P3]=0
2800 Q7=A[P3,P3]*(A[P3,P3]-Q1)+A[P3,P3+1]*A[P3+1,P3]+Q2
2810 Q8=A[P3+1,P3]*(A[P3,P3]+A[P3+1,P3+1]-Q1)
2820 R1=ABS(Q7)+ABS(Q8)
2830 IF R1<>0 THEN 2860
2840 R2=A[P5,P5-1]
2850 GOTO 2760
2860 Q9=A[P3+2,P3+1]*A[P3+1,P3]
2870 R2=0
2880 P8=P8+1
2890 FOR P1=P3 TO P7
2900   P0=P1-1
2910   R4=P1+1
2920   R5=P1+2
2930   IF P1=P3 THEN 2990
2940   Q7=A[P1,P0]
2950   Q8=A[R4,P0]
2960   Q9=0
2970   IF R5>P5 THEN 2990
2980   Q9=A[R5,P0]
2990   Q3=ABS(Q7)+ABS(Q8)+ABS(Q9)
3000   IF Q3=0 THEN 3040
3010   Q7=Q7/Q3
3020   Q8=Q8/Q3
3030   Q9=Q9/Q3
3040   Q1=SQR(Q7*Q7+Q8*Q8+Q9*Q9)
3050   IF Q7<0 THEN 3070
3060   Q1=-Q1
3070   IF P1=P3 THEN 3090
3080   A[P1,P0]=Q1*Q3
3090   IF Q3<>0 THEN 3120
3100   IF P1+3>P5 THEN 3450
3110   GOTO 3410
3120   Q2=1-Q7/Q1
3130   Q1=Q7-Q1
3140   Q7=Q8/Q1
3150   Q8=Q9/Q1
3160   FOR P2=P1 TO P5
3170     Q1=A[P1,P2]+A[R4,P2]*Q7
3180     IF R5>P5 THEN 3200
3190     Q1=Q1+A[R5,P2]*Q8
3200     Q1=Q1*Q2
3210     A[P1,P2]=A[P1,P2]-Q1
3220     A[R4,P2]=A[R4,P2]-Q1*Q7
3230     IF R5>P5 THEN 3250
3240     A[R5,P2]=A[R5,P2]-Q1*Q8
3250   NEXT P2
3260   P4=R5
3270   IF P1<P7 THEN 3290
3280   P4=P5
3290   FOR P2=P3 TO P4
3300     Q1=A[P2,P1]+A[P2,R4]*Q7
3310     IF R5>P5 THEN 3330
3320     Q1=Q1+A[P2,R5]*Q8
3330     Q1=Q1*Q2
3340     A[P2,P1]=A[P2,P1]-Q1
3350     A[P2,R4]=A[P2,R4]-Q1*Q7
```

```
3360      IF R5>P5 THEN 3380
3370      A[P2,R5]=A[P2,R5]-Q1*Q8
3380    NEXT P2
3390    IF P1+3>P5 THEN 3450
3400    Q1=-A[P1+3,R5]*Q8*Q2
3410    P0=P1+3
3420    A[P0,P1]=Q1
3430    A[P0,R4]=Q1*Q7
3440    A[P0,R5]=Q1*Q8+A[P0,R5]
3450  NEXT P1
3460  IF P8>P6 THEN 3750
3470  GOTO 2650
3480  E0[P5]=A[P5,P5]
3490  E1[P5]=0
3500  P[P5,1]=1
3510  REM  PRINT  P5, E0(P5)*Q4, E1(P5)*Q4
3520  P5=P3
3530  GOTO 2650
3540  R1=.5*(A[P3,P3]+A[P5,P5])
3550  Q1=.5*(A[P5,P5]-A[P3,P3])
3560  Q1=Q1*Q1+A[P3,P5]*A[P5,P3]
3570  P[P3,1]=1
3580  P[P5,1]=1
3590  IF Q1<0 THEN 3660
3600  R3=SQR(Q1)
3610  E0[P3]=R1-R3
3620  E0[P5]=R1+R3
3630  E1[P3]=0
3640  E1[P5]=0
3650  GOTO 3710
3660  R3=SQR(-Q1)
3670  E0[P3]=R1
3680  E1[P3]=R3
3690  E0[P5]=R1
3700  E1[P5]=-R3
3710  REM  PRINT P3, E0(P3)*Q4, E1(P3)*Q4      PRINTS EIGENVALUES
3720  REM  PRINT P5, E0(P5)*Q4, E1(P5)*Q4      AS FOUND
3730  P5=P5-2
3740  GOTO 2650
3750  RETURN
3760  REM  ********** END OF EIGENVALUE **********
3770  REM *** PDIFEQ6**********************************************************
3780  REM  ************************************************************
3790  REM
3800  FOR P1=1 TO N
3810    P6=N-P1+1
3820    IF P1<=P4 THEN 3860
3830    P3=P3+1
3840    P5=N-P4
3850    P4=P4+Q[P3,5]
3860    IF P[P6,1]=0 THEN 3960
3870    IF E1[P6]<>0 THEN 3960
3880    FOR P7=1 TO P5
3890      FOR P0=P7 TO P5
3900        A[P7,P0]=E3[P7,P0]
3910      NEXT P0
3920      IF P7=1 THEN 3940
```

```
3930      A[P7,P7-1]=P[P7-1,3]
3940    NEXT P7
3950    GOSUB 4030
3960  NEXT P1
3970  P3=1
3980  P8=0
3990  P4=Q[1,5]
4000  P5=N
4010  GOTO 5060
4020  REM  ************ FINDS A REAL EIGENVECTOR **********
4030  E2[1,P6]=1
4040  IF P5=1 THEN 4990
4050  R6=E0[P6]
4060  IF P6=P5 THEN 4150
4070  R3=P6+1
4080  Q7=0
4090  FOR R1=R3 TO P5
4100    IF R6<>E0[R1] THEN 4130
4110    IF E1[R1]<>0 THEN 4130
4120    Q7=Q7+3
4130  NEXT R1
4140  R6=R6+Q7*Q6
4150  FOR R3=1 TO P5
4160    A[R3,R3]=A[R3,R3]-R6
4170  NEXT R3
4180  R3=P5-1
4190  FOR R1=1 TO R3
4200    R4=R1+1
4210    Q[R1,3]=0
4220    IF A[R4,R1]<>0 THEN 4260
4230    IF A[R1,R1]<>0 THEN 4380
4240    A[R1,R1]=Q5
4250    GOTO 4380
4260    IF ABS(A[R1,R1])>=ABS(A[R4,R1]) THEN 4330
4270    Q[R1,3]=1
4280    FOR R2=R1 TO P5
4290      Q7=A[R1,R2]
4300      A[R1,R2]=A[R4,R2]
4310      A[R4,R2]=Q7
4320    NEXT R2
4330    Q7=-A[R4,R1]/A[R1,R1]
4340    A[R4,R1]=Q7
4350    FOR R2=R4 TO P5
4360      A[R4,R2]=A[R4,R2]+Q7*A[R1,R2]
4370    NEXT R2
4380  NEXT R1
4390  IF A[P5,P5]<>0 THEN 4410
4400  A[P5,P5]=Q5
4410  FOR R1=1 TO N
4420    IF R1>P5 THEN 4450
4430    Q[R1,4]=1
4440    GOTO 4460
4450    Q[R1,4]=0
4460  NEXT R1
4470  Q3=.01/(Q6*N)
4480  R5=0
4490  P0=1
```

```
4500 Q7=0
4510 FOR R1=1 TO P5
4520   R2=P5-R1+1
4530   Q1=Q[R2,4]
4540   IF R2=P5 THEN 4580
4550   FOR R3=R2+1 TO P5
4560     Q1=Q1-Q[R3,4]*A[R2,R3]
4570   NEXT R3
4580   Q[R2,4]=Q1/A[R2,R2]
4590   Q9=ABS(Q[R2,4])
4600   IF Q7>=Q9 THEN 4620
4610   Q7=Q9
4620 NEXT R1
4630 FOR R1=1 TO P5
4640   Q[R1,4]=Q[R1,4]/Q7
4650 NEXT R1
4660 Q8=0
4670 FOR R1=1 TO P5
4680   Q9=0
4690   FOR R2=R1 TO P5
4700     Q9=Q9+A[R1,R2]*Q[R2,4]
4710   NEXT R2
4720   Q9=ABS(Q9)
4730   IF Q8>=Q9 THEN 4750
4740   Q8=Q9
4750 NEXT R1
4760 IF P0=1 THEN 4780
4770 IF R7<=Q8 THEN 4990
4780 FOR R1=1 TO P5
4790   E2[R1,P6]=Q[R1,4]
4800 NEXT R1
4810 R7=Q8
4820 IF R5=1 THEN 4990
4830 IF P0>6 THEN 5000
4840 P0=P0+1
4850 IF Q7<Q3 THEN 4870
4860 R5=1
4870 R3=P5-1
4880 FOR R1=1 TO R3
4890   R4=R1+1
4900   Q7=Q[R4,4]
4910   IF Q[R1,3]=0 THEN 4950
4920   Q[R4,4]=Q[R1,4]+Q[R4,4]*A[R4,R1]
4930   Q[R1,4]=Q7
4940   GOTO 4960
4950   Q[R4,4]=Q[R4,4]+Q[R1,4]*A[R4,R1]
4960 NEXT R1
4970 GOTO 4500
4980 REM  ***********
4990 P[P6,1]=2
5000 IF P5=N THEN 5040
5010 FOR R1=P5+1 TO N
5020   E2[R1,P6]=0
5030 NEXT R1
5040 RETURN
5050 REM  ******** END REAL EIGENVECTORS **********
5060 REM  ************************************************************
```

```
5070 REM  ***********UNSCALE EIGENVECTORS ***********
5080 REM IF P1 THEN 1880
5090 FOR P1=1 TO N
5100   FOR P2=P1 TO N
5110     A[P1,P2]=0
5120     A[P2,P1]=0
5130   NEXT P2
5140   A[P1,P1]=1
5150 NEXT P1
5160 IF N<=2 THEN 5290
5170 FOR P3=1 TO N-2
5180   P4=P3+1
5190   FOR P2=2 TO N
5200     Q1=0
5210     FOR P1=P4 TO N
5220       Q1=Q1+E3[P1,P3]*A[P2,P1]
5230     NEXT P1
5240     FOR P1=P4 TO N
5250       A[P2,P1]=A[P2,P1]-E3[P1,P3]*Q1
5260     NEXT P1
5270   NEXT P2
5280 NEXT P3
5290 P8=1
5300 FOR P1=1 TO N
5310   E5=P1-1
5320   P4=0
5330   IF E1[P1]=0 THEN 5380
5340   P4=1
5350   IF P8=0 THEN 5380
5360   P8=0
5370   GOTO 5850
5380   FOR P2=1 TO N
5390     Q1=0
5400     Q2=0
5410     FOR P3=1 TO N
5420       Q3=A[P2,P3]
5430       Q1=Q1+Q3*E2[P3,P1]
5440       IF P4=0 THEN 5460
5450       Q2=Q2+Q3*E2[P3,E5]
5460     NEXT P3
5470     Q[P2,4]=Q1/P[P2,2]
5480     IF P4=0 THEN 5500
5490     P[P2,3]=Q2/P[P2,2]
5500   NEXT P2
5510   IF P4=1 THEN 5630
5520   Q1=0
5530   FOR P5=1 TO N
5540     Q1=Q1+Q[P5,4]**2
5550   NEXT P5
5560   Q1=SQR(Q1)
5570   FOR P5=1 TO N
5580     E2[P5,P1]=Q[P5,4]/Q1
5590     E3[P5,P1]=0
5600   NEXT P5
5610   E0[P1]=E0[P1]*Q4
5620   GOTO 5850
5630   P8=1
```

```
5640   E0[P1]=E0[P1]*Q4
5650   E0[E5]=E0[P1]
5660   E1[P1]=E1[P1]*Q4
5670   E1[E5]=-E1[P1]
5680   Q7=0
5690   FOR P2=1 TO N
5700     Q8=Q[P2,4]**2+P[P2,3]**2
5710     IF Q7>=Q8 THEN 5740
5720     Q7=Q8
5730     P4=P2
5740   NEXT P2
5750   Q3=Q[P4,4]
5760   Q8=P[P4,3]
5770   FOR P2=1 TO N
5780     Q1=Q[P2,4]
5790     Q2=P[P2,3]
5800     E2[P2,P1]=(Q1*Q3+Q2*Q8)/Q7
5810     E3[P2,P1]=(Q2*Q3-Q1*Q8)/Q7
5820     E2[P2,E5]=E2[P2,P1]
5830     E3[P2,E5]=-E3[P2,P1]
5840   NEXT P2
5850 NEXT P1
5860 REM
5870 REM  ****** PRINT EIGEN -VALUES AND -VECTORS ********
5880 E5=0
5890 E6=0
5900 GOTO 5920
5910 PRINT "REAL EIGEN -VALUES AND -VECTORS"
5920 FOR P1=1 TO N
5930   IF E1[P1]<>0 THEN 6070
5940   IF P[P1,1]=0 THEN 6070
5950   REM PRINT
5960   REM PRINT "# ";P1;"   -VALUE =   ";E0[P1]
5970   E5=E5+1
5980   REM PRINT "       -VECTOR - ";
5990   IF P[P1,1]<>2 THEN 6060
6000   GOTO 6040
6010   FOR P2=1 TO N
6020     PRINT "  ";E2[P2,P1]
6030   NEXT P2
6040   E6=E6+1
6050   GOTO 6070
6060   PRINT "  NOT FOUND"
6070 NEXT P1
6080 IF E5=N THEN 6280
6090 PRINT
6100 PRINT "COMPLEX EIGEN -VALUES AND -VECTORS"
6110 FOR P1=1 TO N
6120   IF E1[P1]=0 THEN 6270
6130   IF P[P1,1]=0 THEN 6270
6140   PRINT
6150   PRINT
6160   PRINT "# ";P1;"   -VALUE  =    ";E0[P1],E1[P1]
6170   E5=E5+1
6180   PRINT "      -VECTOR = ";
6190   PRINT "       -VECTOR =";
6200   IF P[P1,1]<>2 THEN 6260
```

```
6210   FOR P2=1 TO N
6220     PRINT "  ";E2[P2,P1],E3[P2,P1]
6230   NEXT P2
6240   E6=E6+1
6250   GOTO 6270
6260   PRINT "  NOT FOUND"
6270 NEXT P1
6280 PRINT
6290 IF E5<N THEN 6320
6300 PRINT "ALL EIGENVALUES WERE FOUND."
6310 GOTO 6330
6320 PRINT N-E5;" EIGENVALUES WERE NOT FOUND."
6330 IF E6<E5 THEN 6360
6340 PRINT "AN EIGENVECTOR WAS FOUND FOR ALL KNOWN EIGENVALUES."
6350 GOTO 6400
6360 PRINT E5-E6;" EIGENVECTORS WERE NOT FOUND FOR KNOWN -VALUES."
6370 END
6380 REM FINDING PARTICULAR SOLUTION
6390 REM ************************************************************
6400 IF Q4$="N" THEN 6430
6410 PRINT "EIGENVECTOR MATRIX"
6420 MAT PRINT E2
6430 MAT Y=E2
6440 GOSUB 6980
6450 X3=A1
6460 MAT F=INV(E2)
6470 MAT Y=F
6480 GOSUB 6980
6490 X4=A1
6500 IF Q4$="N" THEN 6550
6510 REM PRINT "INVERTED EIGENVECTOR MATRIX"
6520 REM MAT PRINT F
6530 PRINT "LARGEST ELEMENT OF EIGENVECTOR MATRIX ";X3
6540 PRINT "LARGEST ELEMENT OF INVERTED MATRIX ";X4
6550 X5=X3*X4
6560 PRINT "CONDITION FACTOR ";X5
6570 IF Z8=1 THEN 6610
6580 PRINT "INPUT INITIAL CONDITIONS"
6590 MAT INPUT Z3
6600 MAT F1=ZER
6610 MAT F1=F*Z3
6620 IF Q4$="N" THEN 6680
6630 PRINT "CONSTANTS"
6640 MAT PRINT F1
6650 PRINT "FOR INITIAL CONDITIONS"
6660 MAT PRINT Z3
6670 PRINT "THE SOLUTION IS "
6680 FOR I=1 TO N
6690   IF Q4$="N" THEN 6710
6700   PRINT "Y(";I;")=";
6710   FOR J=1 TO N
6720     F2=F1[J]*E2[I,J]
6730     F[I,J]=F1[J]*E2[I,J]
6740     IF Q4$="N" THEN 6760
6750     PRINT F2;"*EXP(";E0[J];"*X)+"
6760   NEXT J
6770   IF Q4$="N" THEN 6790
```

```
6780   PRINT "-----------------"
6790 NEXT I
6800 IF Z9=0 THEN Z9=2
6810 IF Z9=1 OR Z9=3 THEN Z6=1
6820 IF Z9=1 OR Z9=3 THEN Z9=2
6830 GOTO 6880
6840 INPUT "New initials(1),Print(2),Constants(3),Range(4),End(5) ",Z9
6850 Z8=0
6860 IF Z9=4 THEN Z5=0
6870 IF Z9=4 THEN Z9=2
6880 IF Z9<>1 THEN 6930
6890 MAT F=Y
6900 PRINT "Old initial conditions:"
6910 MAT PRINT Z3
6920 GOTO 6580
6930 IF Z9=2 THEN 7080
6940 IF Z9=3 THEN Z8=1
6950 IF Z9=3 THEN Z6=1
6960 IF Z9=3 THEN 9090
6970 END
6980 A1=0
6990 FOR I=1 TO N
7000   FOR J=1 TO N
7010     IF A1>ABS(Y[I,J]) THEN 7030
7020     A1=ABS(Y[I,J])
7030   NEXT J
7040 NEXT I
7050 RETURN
7060 REM ************************************************************
7070 REM DETAILED RESULTS PRINTOUT ROUTINE
7080 INPUT "Print to file as well? Y/N ",Q1$
7090 IF Q1$="N" THEN 7290
7100 INPUT "File name ",N2$
7110 CREATE X,N2$,1000
7120 IF X=0 THEN 7150
7130 PRINT "File not created !"
7140 GOTO 6840
7150 ASSIGN N2$,2,X
7160 IF X=0 THEN 7190
7170 PRINT "Something wrong with file !"
7180 GOTO 6840
7190 PRINT #2;N1,N,N4
7200 PRINT #2;"V"
7210 MAT PRINT #2;V
7220 PRINT #2;"Z"
7230 MAT PRINT #2;Z3
7240 PRINT #2;"W",Z7
7250 PRINT #2;"X"
7260 FOR I=1 TO N9
7270   PRINT #2;X[I]
7280 NEXT I
7290 IF Z5=1 THEN 7350
7300 INPUT "Time ---->? ",X9
7310 INPUT "STEP ",X8
7320 Z5=1
7330 N2=X9+1+(1/X8-1)*X9
7340 REDIM W[N2,N1],W1[N2,N1],T[N2]
```

```
7350 IF Q1$="Y" THEN PRINT #2;"D",N2
7360 PRINT &
    "Time              Concentration in compartments          "
7370 PRINT &
    "-----------------------------------------------------------"
7380 I1=0
7390 FOR I=0 TO X9 STEP X8
7400   I1=I1+1
7410   FOR J=1 TO N1
7420     Y4[J]=0
7430     FOR J1=1 TO N
7440       Y4[J]=Y4[J]+F[J,J1]*EXP(E0[J1]*I)
7450     NEXT J1
7460   NEXT J
7470   IF Q3$="Y" THEN Y5[I1]=(Y4[3]*V[3]+Y4[5]*V[5])/(V[3]+V[5])
7480   IF Q1$="N" THEN 7500
7490   PRINT #2;I
7500   PRINT I,
7510   T[I1]=I
7520   FOR J=1 TO N1
7530     PRINT Y4[J];
7540     W[I1,J]=Y4[J]
7550     IF Q1$="N" THEN 7570
7560     PRINT #2;Y4[J]
7570   NEXT J
7580   PRINT
7590 NEXT I
7600 PRINT &
    "-----------------------------------------------------------"
7610 IF Z6=0 THEN 7720
7620 PRINT "Difference, new-old"
7630 PRINT &
    "-----------------------------------------------------------"
7640 FOR I=1 TO N2
7650   PRINT USING "#,2D.D,4X";T[I]
7660   FOR J=1 TO N1
7670     PRINT USING "#,M4D.2D,3X";W[I,J]-W1[I,J]
7680   NEXT J
7690   PRINT
7700 NEXT I
7710 PRINT &
    "-----------------------------------------------------------"
7720 MAT W1=W
7730 Z6=0
7740 IF Q3$<>"Y" THEN 7810
7750 PRINT "Concentration in combined hepatopancreas compartment"
7760 FOR I=1 TO N2
7770   PRINT Y5[I]
7780   IF Q1$<>"Y" THEN 7800
7790   PRINT #2;Y5[I]
7800 NEXT I
7810 IF Q1$="N" THEN 6840
7820 PRINT "Results based on file ";N1$;" written also to file ";N2$
7830 GOTO 6840
7840 REM ****** CENTRAL COMPARTMENT MODEL INPUT *********
7850 MAT X=ZER
7860 MAT A=ZER
```

```
7870 MAT V=ZER
7880 DATA "k01","k10","k12","k21","k20"
7890 DATA "k23","k32","k30","k24","k42","k40"
7900 DATA "k25","k52","k50","k26","k62","k60"
7910 DATA "k27","k72","k70","k28","k82","k80"
7920 DATA "k29","k92","k90"
7930 MAT READ K$
7940 INPUT "Explanation ? Y/N ",Q1$
7950 IF Q1$="Y" THEN GOSUB 8860
7960 INPUT "Constants manually? Y/N ",Q1$
7970 IF Q1$="N" THEN 8010
7980 INPUT "Dual hepato? Y/N ",Q3$
7990 IF Q3$="Y" THEN GOSUB 9200
8000 GOTO 8100
8010 INPUT "CONSTANTS FILE ",N1$
8020 ASSIGN N1$,1,Z
8030 IF Z=0 THEN 8050
8040 GOTO 8010
8050 READ #1;N1,N,N4
8060 IF N1<>N4 THEN Q3$="Y"
8070 Q2$="Y"
8080 IF N1<>N THEN Q2$="N"
8090 GOTO 8180
8100 IF Q3$="N" THEN 8130
8110 N1=5
8120 GOTO 8150
8130 INPUT "Number of compartments (water does not count) ",N1
8140 N4=N1
8150 INPUT "Excretion? Y/N ",Q2$
8160 N=N1+1
8170 IF Q2$="Y" THEN N=N1
8180 REDIM A[N,N],V[N1],Y4[N1],Z3[N]
8190 REDIM F1[N],F[N,N],Y[N,N]
8195 IF N1=1 THEN REDIM V[2]
8196 IF N1=1 THEN V[1]=V[2]=1
8200 N9=5+(N1-2)*3
8210 IF Q1$="Y" THEN 8330
8220 IF TYP(1)=3 THEN 8370
8230 IF TYP(1)=2 THEN READ #1;F$
8240 IF LEN(F$)=1 THEN 8270
8250 ADVANCE #1;1,V
8260 GOTO 8220
8270 IF F$="V" THEN GOSUB 9250
8280 IF F$="Z" THEN GOSUB 9270
8290 IF F$="X" THEN GOSUB 9360
8300 IF F$="V" OR F$="Z" OR F$="X" THEN 8220
8310 ADVANCE #1;1,X
8320 GOTO 8220
8330 FOR I=1 TO N9
8340    PRINT K$[I],
8350    INPUT X[I]
8360 NEXT I
8370 IF V[1]<>0 THEN 8420
8375 IF N1=1 THEN 8420
8380 FOR I=1 TO N1
8390    PRINT "Volume of compartment ";I;
8400    INPUT V[I]
```

```
8410 NEXT I
8420 IF Q2$="Y" THEN 8440
8430 A[1,N]=X[1]/V[1]
8440 A[1,1]=-(X[2]+X[3])
8445 IF N1=1 THEN 8610
8450 A[2,2]=-(X[4]+X[5]+X[6]+X[9]+X[12]+X[15]+X[18]+X[21]+X[24])
8460 A[1,2]=V[2]*X[4]/V[1]
8470 A[2,1]=V[1]*X[3]/V[2]
8480 FOR I=3 TO N1
8490   IF Q3$<>"Y" THEN 8510
8500   IF I=5 THEN 8540
8510   A[2,I]=V[I]*X[3*I-2]/V[2]
8520   A[I,2]=V[2]*X[3*I-3]/V[I]
8530   A[I,I]=-(X[3*I-2]+X[3*I-1])
8540 NEXT I
8550 IF Q3$<>"Y" THEN 8610
8560 A[5,5]=-X[13]
8570 A[3,5]=X[13]*V[5]/V[3]
8580 A[3,3]=A[3,3]-X[12]
8590 A[2,2]=A[2,2]+X[12]
8600 A[5,3]=X[12]*V[3]/V[5]
8610 IF Q2$="Y" THEN 8670
8620 INPUT "Exponential decrease in Cw? Y/N ",Q5$
8630 IF Q5$="N" THEN 8670
8640 INPUT "Rate of exponential decrease ",A[N,N]
8650 IF A[N,N]>0 THEN A[N,N]=-A[N,N]
8660 Z7=A[N,N]
8670 IF Q4$="N" THEN 8840
8680 FOR I=1 TO N9
8690   PRINT K$[I],X[I]
8700 NEXT I
8710 PRINT "---------------"
8720 PRINT "VOLUMES"
8730 FOR I=1 TO N1
8740   PRINT V[I];
8750 NEXT I
8760 PRINT
8770 PRINT "DIFEQ MATRIX"
8780 FOR I=1 TO N
8790   FOR J=1 TO N
8800     PRINT A[I,J];
8810   NEXT J
8820   PRINT
8830 NEXT I
8840 IF Z9=3 THEN 600
8850 RETURN
8860 PRINT &
    "This program constructs the differential equations matrix."
8870 PRINT &
    "It assumes that the system consists of one ENTRY, one CENTRAL,"
8880 PRINT "and  up to 7 PERIPHERAL compartments."
8890 PRINT
8900 PRINT &
    "The rate constants subscripts refer to the numbers of the "
8910 PRINT &
    "ORIGINATING and the RECEIVING compartment, respectively. For"
8920 PRINT "example k01 is the rate constant for the transfer from"
```

```
8930 PRINT "compartment 0 to compartment 1."
8940 PRINT
8950 PRINT &
    "Compartment 0 is water, compartment 1 is the ENTRY compartment,"
8960 PRINT "compartment 2 is the CENTRAL compartment."
8970 PRINT
8980 PRINT &
    "Volumes or weights of compartments must be given and initial"
8990 PRINT &
    "conditions must be specified starting with compartment 1 and"
9000 PRINT "ending with water (compartment 0)."
9010 PRINT
9020 PRINT &
    "The concentration in water Cw may be either constant or may"
9030 PRINT "decrease exponentially. In the latter case, rate of the"
9040 PRINT "exponential decrease must be entered."
9050 PRINT
9060 PRINT "Dual hepato assumes 4 compartments with hepatopancreas"
9070 PRINT "(compartment 3) composed of TWO compartments (3 and 5)."
9080 RETURN
9090 REM ******** CHANGE CONSTANTS ROUTINE
9100 MAT A=ZER
9110 FOR I=1 TO N9
9120   PRINT I;K$[I],X[I]
9130 NEXT I
9140 INPUT "Change constant number (0 if done )",I
9150 IF I>N9 THEN 9140
9160 IF I=0 THEN 8420
9170 INPUT K1
9180 X[I]=K1
9190 GOTO 9140
9200 K$[12]="k35"
9210 K$[13]="k53"
9220 K$[14]="k50"
9230 N4=0
9240 RETURN
9250 MAT READ #1;V
9260 RETURN
9270 FOR I=1 TO N
9275   IF TYP(1)=1 THEN 9280
9277   Z8=0
9278   GOTO 9350
9280   READ #1;Z3[I]
9290 NEXT I
9300 IF TYP(1)=2 THEN 9340
9310 ADVANCE #1;1,V1
9320 Z8=0
9330 GOTO 9350
9340 Z8=1
9350 RETURN
9360 FOR I=1 TO N9
9370   READ #1;X[I]
9380 NEXT I
9390 RETURN
```

```
**************************************************************


>>>>>>>>>>>>>MCMRAT<<<<<<<<<<<<<<<<<
   10 LONG C[10,30],C1[30,10],C2[10,10],C3[10,10],C4[30,10]
   20 LONG Y[10,30],K[11,11]
   30 LONG D[10,30],Y1[10,30]
   40 DIM D$[5],P[5]
   50 DIM V[10],X[26]
   60 DIM N1$[10],K$[14,3]
   70 DATA "k01","k10","k12","k21","k20","k23","k32","k30","k24","k42",&
     "k40"
   80 DATA "k25","k52","k50"
   90 MAT READ K$
  100 REM Y[compartments,measurements]=K[compartments,compartments]*
  110 REM                              *C[compartments,measurements]
  120 MAT P=ZER
  130 REM K = Y*C1*(C*C1)EXP(-1)
  140 REM C1<- transp C,C2<- (C*C1), C3<- 1/C2,C4<-C1*C3
  150 FILES *,*
  160 INPUT "Write file (1), calculate (2), explanation (3) ",Q1
  170 IF Q1=3 THEN 1660
  180 INPUT "Print intermediate matrices? Y/N ",Q2$
  190 IF Q1=1 THEN 1220
  200 INPUT "Filename ",N1$
  210 ASSIGN N1$,1,V1
  220 IF V1=0 THEN 250
  230 PRINT "SOMETHING WRONG "
  240 STOP
  250 READ #1;N1,N,N2
  260 F1=1
  270 IF N=N1 THEN F1=2
  280 F3=0
  290 REM F3 IS DEGENERATE MODEL FLAG
  300 REM N1 number of compartments; N=N1+1 for uptake,else N=N1
  310 REM N2 number of points
  320 REDIM C[N,N2],C1[N2,N],C2[N,N],C3[N,N],C4[N2,N],Y[N,N2],K[N,N]
  330 REDIM V[N],X[5+(N1-2)*3]
  340 MAT X=ZER
  350 MAT READ #1;C
  360 MAT READ #1;Y
  370 PRINT "THE NUMBER OF COMPARTMENTS IS ";N1
  380 INPUT "ANALYZE DEGENERATE MODELS? YES(1),NO(2) ",Q3
  390 IF Q3=1 THEN GOSUB 1920
  400 MAT C1=TRN(C)
  410 MAT C2=C*C1
  420 MAT C3=INV(C2)
  430 MAT C4=C1*C3
  440 MAT K=Y*C4
  450 IF Q2$="N" THEN 480
  460 MAT PRINT K
  470 PRINT "--------------------"
  480 IF F1=2 THEN 600
  490 REM Zero all elements in n-th column except for first row
  500 FOR I=2 TO N
  510   IF K[I,N]=0 THEN 550
  520   FOR J=1 TO N
```

```
530      K[I,J]=K[I,J]-K[I,N]/K[1,N]*K[1,J]
540    NEXT J
550  NEXT I
560  IF Q2$="N" THEN 600
570  MAT PRINT K
580  PRINT "--------------------"
590  REM Zero elements of first column starting with the 3-rd row
600  FOR I=3 TO N
610    K=K[I,1]
620    FOR J=1 TO N
630      K[I,J]=K[I,J]-K/K[2,1]*K[2,J]
640    NEXT J
650  NEXT I
660  IF Q2$="N" THEN 710
670  MAT PRINT K
680  PRINT "-----------------------"
690  IF N1=1 THEN 760
700  REM Zero element of first row in column 3
710  I=3
715  IF F3=0 THEN 720
716  IF D1=1 THEN 760
720  IF K[2,3]=0 THEN 760
730  FOR J=1 TO N
740    K[1,J]=K[1,J]-K[1,I]/K[2,I]*K[2,J]
750  NEXT J
760  FOR I=1 TO N
770    FOR J=1 TO N
780      PRINT USING "#,M3D.2D,4X";K[I,J]
790    NEXT J
800    PRINT
810  NEXT I
820  INPUT "Constants calculation(1),NEW calcn(2),file(3),end(4) ",Q1
830  IF Q1=2 THEN 200
840  IF Q1=3 THEN 1220
850  IF Q1=4 THEN 1210
860  IF F3=0 THEN 890
865  N1=LEN(D$)
870  IF N1=1 THEN PRINT "Not necessary"
875  IF N1=1 THEN GOTO 820
890  FOR I=1 TO N1
900    PRINT "Compartment ";I
910    INPUT V[I]
920  NEXT I
930  I=1
940  IF F1=2 THEN 970
950  X[I]=K[1,N]*V[1]
960  GOTO 980
970  X[I]=0
980  I=I+1
990  X[4]=K[1,2]*V[1]/V[2]
1000 X[3]=K[2,1]*V[2]/V[1]
1010 X[2]=-K[1,1]-X[3]
1015 X[5]=-K[2,2]-X[4]
1020 IF N1=2 THEN 1170
1030 X[7]=V[2]/V[3]*K[2,N1]
1040 X[6]=V[3]/V[2]*K[3,2]
1050 X[5]=-K[2,2]-X[4]-X[6]
```

```
1060 X[8]=-K[3,3]-X[7]
1070 IF N1=3 THEN 1170
1080 X[9]=V[4]/V[2]*K[4,2]
1090 X[10]=V[2]/V[4]*K[2,4]
1100 X[5]=X[5]-X[11]
1110 X[11]=-K[4,4]-X[10]
1120 IF N1=4 THEN 1170
1130 X[12]=V[5]/V[2]*K[5,2]
1140 X[13]=V[2]/V[5]*K[2,5]
1150 X[14]=-K[5,5]-X[13]
1160 X[5]=X[5]-X[12]
1170 FOR I=1 TO 5+(N1-2)*3
1180   PRINT K$[I],X[I]
1190 NEXT I
1200 GOTO 820
1210 END
1220 INPUT "Filename ",N1$
1230 CREATE V2,N1$,200
1240 IF V2=0 THEN 1290
1250 IF V2=1 THEN PRINT "Duplicate file "
1260 IF V2=1 THEN 1220
1270 PRINT "File not created"
1280 STOP
1290 ASSIGN N1$,1,V1
1300 IF V1=0 THEN 1330
1310 PRINT "FILE NOT ASSIGNED"
1320 STOP
1330 INPUT "Number of compartments ",N1
1340 N=N1
1350 INPUT "Uptake (1), Excretion (2) ",F1
1360 IF F1=1 THEN N=N+1
1370 INPUT "Number of points ",N2
1380 PRINT #1;N1,N,N2
1390 PRINT "CONCENTRATIONS "
1400 FOR I=1 TO N1
1410   PRINT "Compartment ";I
1420   FOR J=1 TO N2
1430     INPUT "Concentration ",C
1440     PRINT #1;C
1450   NEXT J
1460 NEXT I
1470 IF F1=2 THEN 1520
1480 INPUT "Concentration in water ",C
1490 FOR I=1 TO N2
1500   PRINT #1;C
1510 NEXT I
1520 PRINT "SLOPES "
1530 FOR I=1 TO N1
1540   PRINT "Compartment ";I
1550   FOR J=1 TO N2
1560     INPUT "Slope ",S
1570     PRINT #1;S
1580   NEXT J
1590 NEXT I
1600 IF F1=2 THEN 1640
1610 FOR I=1 TO N2
1620   PRINT #1;0
```

```
1630 NEXT I
1640 RESTORE #1
1650 GOTO 250
1660 PRINT "This program attempts to calculate rate constants from"
1670 PRINT "the differential equations by a least square fit."
1680 PRINT "Required input consists of concentrations in individual"
1690 PRINT "compartments and their derivatives (slopes) at the same"
1700 PRINT "times."
1710 PRINT "The most convenient procedure to obtain these values is"
1720 PRINT "to interpolate between experimental points by a cubic"
1730 PRINT "spline with some data smoothing and to estimate both"
1740 PRINT "concentrations and their derivatives from the spline fit."
1750 PRINT &
   "The data must be first written to a file [use option (1)]."
1760 PRINT "The number of points must at least equal to the number "
1770 PRINT "of compartments."
1780 PRINT "Compartment volumes are needed to calculate the rate"
1790 PRINT "constants."
1800 PRINT "THIS OPTION IS AVAILABLE FOR A MAXIMUM OF 5 COMPARTMENTS"
1810 PRINT "IN A MAMMILLARY (FROM COMPARTMENT 2) ARRANGEMENT."
1820 PRINT "THE SYSTEM MATRICES MAY BE ESTIMATED FOR UP TO 10"
1830 PRINT "COMPARTMENTS, BUT KEEP IN MIND THAT WITH INCREASING"
1840 PRINT "NUMBER OF COMPARTMENTS THE CALCULATIONS ARE BECOMING"
1850 PRINT "INCREASINGLY MEANINGLESS."
1860 PRINT "It is also possible to use fewer compartments than"
1870 PRINT "specified by the data. This may be necessary for"
1880 PRINT "DEGENERATE models for which some exponential terms"
1890 PRINT "decay to zero without being captured adequately by"
1900 PRINT "experimental data."
1910 GOTO 160
1920 INPUT "NUMBER OF COMPARTMENTS ",D1
1930 C=C[N,1]
1940 IF D1=N1 THEN 1920
1950 N=D1
1960 IF F1=1 THEN N=N+1
1970 D$=DEB$(D$)
1980 REDIM P[D1]
1990 INPUT "ENTER DESIRED COMPARTMENTS, I.E. 13 ",D$
2000 FOR I=1 TO LEN(D$)
2010   CONVERT D$[I;1] TO P[I]
2020 NEXT I
2030 REDIM C1[N2,N],C2[N,N],C3[N,N],C4[N2,N],K[N,N]
2040 REDIM D[N,N2],Y1[N,N2]
2050 FOR I=1 TO LEN(D$)
2060   FOR J=1 TO N2
2070     D[I,J]=C[P[I],J]
2080     Y1[I,J]=Y[P[I],J]
2090   NEXT J
2100 NEXT I
2110 FOR J=1 TO N2
2120   D[N,J]=C
2130   Y1[N,J]=0
2140 NEXT J
2150 REDIM C[N,N2],Y[N,N2]
2160 MAT C=D
2170 MAT Y=Y1
2180 F3=1
```

```
2190 RETURN


**************************************************************
  >>>>>>>>>>>>MCMSX<<<<<<<<<<<<<<<<<<<<
  10 DIM A[10,10],D[30,10],Z3[10]
  20 DIM N1$[10],N2$[10],N3$[10],X[26]
  30 DIM F$[10],A1[27,27],A2[27,3]
  40 DIM K[10],K0[10],K1[10],K2[10],K3[10],K4[10],K5[10]
  50 DIM L[10],L0[10],L1[10],E[10]
  60 DIM Y0[10],Y3[10],Y4[10],Y9[10]
  70 DIM F[10,10],Y1[10,10],F1[10]
  80 DIM X1[30]
  90 DIM Y5[30,10]
 100 DIM D1[30],D2[30]
 110 INTEGER N,N1,N2,N3,N4,N5,N8,N9,I,I7,I8,I9,C1,C3,C4,C9,J,D1,F1,Z9,&
    K
 120 INTEGER Z8,W1,W2,W4,V1,V2,V3,V4
 130 INTEGER F2
 140 MAT X=ZER
 150 REM RUNGE-KUTTA PARAMETERS
 160 E1=5.9E-8
 170 H9=26*E1
 180 REM COEFFS. FOR SIMPLEX CHANGES
 190 C1=1
 200 C2=.5
 210 C3=2
 220 S1=1E10
 230 C9=0
 240 S6=1E10
 250 C8=.0001
 260 Z9=0
 270 INPUT "Data input file ",N1$
 280 INPUT "Constants input file ",N2$
 290 INPUT "Data output file ",N3$
 300 INPUT "Number of iterations ",C4
 310 INPUT "Initial simplex span ",C7
 320 INPUT "Runge-Kutta tolerance ",T
 330 INPUT "Convergence tolerance ",Z8
 340 FILES *,*,*
 350 ASSIGN N1$,1,V1
 360 ASSIGN N2$,2,V2
 370 CREATE V3,N3$,200
 380 ASSIGN N3$,3,V4
 390 IF V1=0 AND V2=0 AND V3=0 AND V4=0 THEN 450
 400 IF V1<>0 THEN PRINT "Data file not available"
 410 IF V2<>0 THEN PRINT "Constants file not available"
 420 IF V3<>0 THEN PRINT "Output file not created"
 430 IF V4<>0 THEN PRINT "Output file not available"
 440 STOP
 450 READ #1;W1,W2,W4
 460 READ #2;N1,N,N4
 470 IF N1=W1 AND N=W2 AND N4=W4 THEN 500
 480 PRINT "Constants and data file not compatible"
 490 STOP
 500 N9=5+(N1-2)*3
```

```
510 C9=-N9-1
520 REDIM A[N,N],Z3[N],V[N1]
530 REDIM A1[N9+1,N9+1]
540 REDIM A2[N9+1,3]
550 REDIM F[N,N],Y[N,N]
560 REDIM F1[N]
570 REDIM K[N],KO[N],K1[N],K2[N],K3[N],K4[N],K5[N]
580 REDIM L[N],LO[N],L1[N],E[N]
590 REDIM YO[N],Y3[N],Y4[N],Y9[N]
600 MAT A=ZER
610 MAT A1=ZER
620 MAT A2=ZER
630 READ #1;F$
640 MAT READ #1;V
650 READ #1;F$
660 MAT READ #1;Z3
670 READ #1;F$,K1
680 READ #1;F$
690 IF F$="D" THEN 730
700 ADVANCE #1;1,V1
710 IF TYP(1)=2 THEN 680
720 GOTO 700
730 READ #1;N2
740 REDIM D[N2,N1+1],D1[N2],D2[N2],X1[N2],Y5[N2,N1]
750 MAT Y5=ZER
760 FOR I=1 TO N2
770   FOR J=1 TO N1+1
780     READ #1;D[I,J]
790   NEXT J
800 NEXT I
810 FOR I=1 TO N2
820   X1[I]=D[I,1]
830 NEXT I
840 IF N4<>0 THEN 890
850 FOR I=1 TO N2
860   READ #1;D1[I]
870   REM CONCN IN COMBINED HEPATO
880 NEXT I
890 X9=X1[N2]
900 READ #2;F$
910 FOR I=1 TO N9
920   READ #2;X[I]
930   A1[I,1]=X[I]
940 NEXT I
950 PRINT #3;N1,N,N4
960 PRINT #3;"V"
970 MAT PRINT #3;V
980 PRINT #3;"Z"
990 MAT PRINT #3;Z3
1000 PRINT #3;"W",K1
1010 PRINT #3;"D",N2
1020 MAT PRINT #3;D
1030 IF N1=N4 THEN 1050
1040 MAT PRINT #3;D1
1050 GOTO 1320
1060 REM ****************************************
1070 MAT A=ZER
```

```
1080 C9=C9+1
1090 IF N1=N THEN 1110
1100 A[1,N]=X[1]
1110 A[1,1]=-(X[2]+X[3])
1120 A[2,2]=-(X[4]+X[5]+X[6]+X[9]+X[12]+X[15]+X[18]+X[21]+X[24])
1130 A[1,2]=V[2]*X[4]/V[1]
1140 A[2,1]=V[1]*X[3]/V[2]
1150 FOR I=3 TO N1
1160   IF N1=N4 THEN 1180
1170   IF I=5 THEN 1210
1180   A[2,I]=V[I]*X[3*I-2]/V[2]
1190   A[I,2]=V[2]*X[3*I-3]/V[I]
1200   A[I,I]=-(X[3*I-2]+X[3*I-1])
1210 NEXT I
1220 IF N1=N4 THEN 1280
1230 A[5,5]=-X[13]
1240 A[3,5]=X[13]*V[5]/V[3]
1250 A[3,3]=A[3,3]-X[12]
1260 A[2,2]=A[2,2]+X[12]
1270 A[5,3]=X[12]*V[3]/V[5]
1280 IF N1<>N THEN A[N,N]=K1
1290 GOSUB 2930
1300 RETURN
1310 REM ****************************************
1320 REM **********  INITIAL SIMPLEX ***************************************
1330 FOR J=2 TO N9+1
1340   FOR I=1 TO N9
1350     A1[I,J]=C7*RND(0)*A1[I,1]-(C7-2)*RND(0)*A1[I,1]
1360     IF A1[I,J]<0 THEN 1350
1370   NEXT I
1380 NEXT J
1390 REM ********** CALCULATE SS'S  ***************************************
1400 FOR K=1 TO N9+1
1410   FOR I=1 TO N9
1420     X[I]=A1[I,K]
1430   NEXT I
1440   GOSUB 1070
1450   A1[N9+1,K]=S
1460 NEXT K
1470 MAT PRINT A1
1480 REM ****************************************
1490 S9=0
1500 S1=1E10
1510 FOR I=1 TO N9+1
1520   IF S9>A1[N9+1,I] THEN 1550
1530   S9=A1[N9+1,I]
1540   I9=I
1550 NEXT I
1560 FOR I=1 TO N9+1
1570   IF S1<A1[N9+1,I] THEN 1600
1580   S1=A1[N9+1,I]
1590   I7=I
1600 NEXT I
1610 S9=0
1620 FOR I=1 TO N9+1
1630   IF I=I9 THEN 1670
1640   IF S9>A1[N9+1,I] THEN 1670
```

```
1650   S9=A1[N9+1,I]
1660   I8=I
1670 NEXT I
1680 REM ******************CONVERGENCE CHECK ************
1690 S5=S4=0
1700 PRINT C9;
1710 FOR I=1 TO N9+1
1720   S5=S5+A1[N9+1,I]
1730   S4=S4+A1[N9+1,I]**2
1740 NEXT I
1750 S2=S4-S5**2/(N9+1)
1760 IF S2<.0001 THEN 1780
1770 IF SQR(S2/(N9+1))>Z8 THEN 1940
1780 MAT X=ZER
1790 FOR I=1 TO N9
1800   FOR J=1 TO N9+1
1810     X[I]=X[I]+A1[I,J]
1820   NEXT J
1830   X[I]=X[I]/(N9+1)
1840 NEXT I
1850 GOSUB 1070
1860 S4=0
1870 FOR I=1 TO N9+1
1880   S4=S4+(A1[N9+1,I]-S)**2
1890 NEXT I
1900 S4=SQR(S4/(N9+1))
1910 IF S4>Z8 THEN 1940
1920 GOSUB 4110
1930 GOTO 1980
1940 IF C9<C4 THEN 1990
1950 PRINT
1960 PRINT "NOT CONVERGED"
1970 GOSUB 4110
1980 END
1990 REM ****************** CENTROID ********************
2000 FOR I=1 TO N9
2010   A2[I,1]=0
2020   FOR J=1 TO N9+1
2030     IF Z9=1 THEN 2070
2040     REM Reflecting from Nw
2050     IF J=I9 THEN 2090
2060     GOTO 2080
2070     IF J=I8 THEN 2090
2080     A2[I,1]=A2[I,1]+A1[I,J]
2090   NEXT J
2100   A2[I,1]=A2[I,1]/N9
2110 NEXT I
2120 REM ***REFLECTION ****
2130 FOR I=1 TO N9
2140   IF Z9=0 THEN 2170
2150   A2[I,2]=(1+C1)*A2[I,1]-C1*A1[I,I8]
2160   GOTO 2180
2170   A2[I,2]=(1+C1)*A2[I,1]-C1*A1[I,I9]
2180   X[I]=A2[I,2]
2190 NEXT I
2200 IF Z9=1 THEN Z9=0
2210 FOR I=1 TO N9
```

```
2220   IF X[I]<0 THEN Z9=1
2230 NEXT I
2240 IF Z9=1 THEN 2270
2250 GOSUB 1070
2260 GOTO 2290
2270 S=1E7
2280 Z9=0
2290 S6=S
2300 IF S<=A1[N9+1,I7] THEN 2710
2310 IF S<A1[N9+1,I8] THEN 2640
2320 IF S>A1[N9+1,I9] THEN 2480
2330 FOR I=1 TO N9
2340   A1[I,I9]=C2*A2[I,1]+(1-C2)*A2[I,2]
2350   X[I]=A1[I,I9]
2360   IF X[I]<0 THEN Z9=1
2370 NEXT I
2380 IF Z9=1 THEN 2410
2390 GOSUB 1070
2400 GOTO 2430
2410 S=1E7
2420 Z9=0
2430 A1[N9+1,I9]=S
2440 IF S<A1[N9+1,I8] THEN 1490
2450 Z9=1
2460 GOTO 1490
2470 REM ----------------------------------------
2480 FOR I=1 TO N9
2490   A1[I,I9]=C2*A1[I,I9]+(1-C2)*A2[I,1]
2500   REM MID WORST & CENTROID
2510   X[I]=A1[I,I9]
2520   IF X[I]<0 THEN Z9=1
2530 NEXT I
2540 IF Z9=1 THEN 2570
2550 GOSUB 1070
2560 GOTO 2590
2570 S=1E7
2580 Z9=0
2590 IF S<A1[N9+1,I9] THEN 2610
2600 Z9=1
2610 A1[N9+1,I9]=S
2620 GOTO 1490
2630 REM ----------------------------------------
2640 REM REFLECT!
2650 FOR I=1 TO N9
2660   A1[I,I9]=A2[I,2]
2670 NEXT I
2680 A1[N9+1,I9]=S6
2690 GOTO 1490
2700 REM ----------------------------------------
2710 REM EXPANSION
2720 FOR I=1 TO N9
2730   A2[I,3]=C3*A2[I,2]+(1-C3)*A2[I,1]
2740   X[I]=A2[I,3]
2750   IF X[I]<0 THEN Z9=1
2760 NEXT I
2770 IF Z9=1 THEN 2800
2780 GOSUB 1070
```

```
2790 GOTO 2820
2800 S=1E7
2810 Z9=0
2820 IF S<S6 THEN 2860
2830 REM EXPANSION BETTER THAN REFLECTION
2840 GOTO 2640
2850 REM GOING TO REFLECTION
2860 REM EXPAND!
2870 FOR I=1 TO N9
2880   A1[I,I9]=A2[I,3]
2890 NEXT I
2900 A1[N9+1,I9]=S
2910 GOTO 1490
2920 REM ----------------------------------------
2930 REM **********RUNGE-KUTTA ***********
2940 H=.05
2950 F1=0
2960 D1=1
2970 X=0
2980 MAT Y0=Z3
2990 IF X1[1]<>0 THEN 3080
3000 FOR I=1 TO N1
3010   Y5[1,I]=Y0[I]
3020 NEXT I
3030 D1=D1+1
3040 GOTO 3080
3050 IF H>H9 THEN 3080
3060 PRINT "Step size too small"
3070 STOP
3080 H1=H/3
3090 MAT Y9=Y0
3100 MAT Y=A*Y9
3110 MAT K1=(H1)*Y
3120 MAT Y9=Y0+K1
3130 MAT Y=A*Y9
3140 MAT K2=(H1)*Y
3150 MAT K=K1+K2
3160 MAT K=(.5)*K
3170 MAT Y9=Y0+K
3180 MAT Y=A*Y9
3190 MAT K3=(H1)*Y
3200 MAT L=(3)*K1
3210 MAT L0=(9)*K3
3220 MAT K=L+L0
3230 MAT K=(1/8)*K
3240 MAT Y9=Y0+K
3250 MAT Y=A*Y9
3260 MAT K4=(H1)*Y
3270 MAT L1=(12)*K4
3280 MAT K=L-L0
3290 MAT K=K+L1
3300 MAT K=(1/12)*K
3310 MAT Y3=Y0+K
3320 MAT Y9=Y3
3330 MAT Y=A*Y9
3340 MAT K5=(H1)*Y
3350 MAT L=(4)*K4
```

```
3360 MAT K=K1+L
3370 MAT K=K+K5
3380 MAT K=(.5)*K
3390 MAT Y4=Y0+K
3400 MAT E=Y4-Y3
3410 MAT E=(1/5)*E
3420 IF X>=X9 THEN 3860
3430 E9=E8=F2=0
3440 FOR I=1 TO N
3450   IF ABS(E[I])<E8 THEN 3480
3460   E8=ABS(E[I])
3470   IF Y4[I]=0 THEN F2=1
3480 NEXT I
3490 IF F2=1 THEN 3550
3500 FOR I=1 TO N
3510   IF ABS(E[I]/Y4[I])<E9 THEN 3530
3520   E9=ABS(E[I]/Y4[I])
3530 NEXT I
3540 IF F2=0 THEN 3570
3550 IF E8<.0001 THEN 3590
3560 GOTO 3790
3570 IF E9>T THEN 3790
3580 REM ********** Adjust step to data ***************
3590 IF X+H<X1[D1] THEN 3640
3600 H2=H
3610 H=X1[D1]-X
3620 F1=1
3630 REM ************************************************
3640 X=X+H
3650 MAT Y0=Y4
3660 IF F1=0 THEN 3760
3670 REM ************ Write result ***************
3680 FOR I=1 TO N1
3690   Y5[D1,I]=Y0[I]
3700 NEXT I
3710 D1=D1+1
3720 IF D1=N2+1 THEN 3860
3730 H=H2
3740 F1=0
3750 REM ********************************************
3760 IF E9<.5*T THEN 3820
3770 GOTO 3050
3780 REM ************* Decrease step ****************
3790 H=.9*H*(T/E9)**.25
3800 GOTO 3050
3810 REM *************** Increase step ***********************
3820 H=2*H
3830 GOTO 3050
3840 REM **** CALCULATE SUSQ ***
3850 REM ********************************************************
3860 S=0
3870 IF N1=N4 THEN 4030
3880 FOR I=1 TO N2
3890   D2[I]=(Y5[I,3]*V[3]+Y5[I,5]*V[5])/(V[3]+V[5])
3900 NEXT I
3910 FOR I=1 TO 4
3920   IF I=3 THEN 3970
```

```
3930   FOR J=1 TO N2
3940     IF D[J,I+1]<.01 THEN 3960
3950     S=S+((D[J,I+1]-Y5[J,I])/D[J,I+1])**2
3960   NEXT J
3970 NEXT I
3980 FOR I=1 TO N2
3990   IF D1[I]<.01 THEN 4010
4000   S=S+((D1[I]-D2[I])/D1[I])**2
4010 NEXT I
4020 GOTO 4090
4030 FOR I=1 TO N1
4040   FOR J=1 TO N2
4050     IF D[J,I+1]<.001 THEN 4070
4060     S=S+((Y5[J,I]-D[J,I+1])/D[J,I+1])**2
4070   NEXT J
4080 NEXT I
4090 RETURN
4100 REM **** WRITE RESULTS TO FILE *******
4110 PRINT #3;"X"
4120 FOR I=1 TO N9
4130   PRINT #3;A1[I,I7]
4140   X[I]=A1[I,I7]
4150 NEXT I
4160 GOSUB 1070
4170 PRINT #3;"S",C9
4180 MAT PRINT #3;A1
4190 MAT PRINT #3;Y5
4200 IF N1=N4 THEN 4220
4210 MAT PRINT #3;D2
4220 PRINT #3;END
4230 PRINT "Time        Concentration ( Data <-> Calculated)"
4240 PRINT "-------------------------------------------------"
4250 FOR I=1 TO N2
4260   FOR J=1 TO N1+1
4270     IF J=1 THEN PRINT USING "#,2D.D";D[I,1]
4280     IF J=1 THEN 4300
4290     PRINT USING "#,3X,4D.2D,2X,4D.2D";D[I,J],Y5[I,J-1]
4300   NEXT J
4310   PRINT
4320 NEXT I
4330 PRINT "-----------------------------------------"
4340 PRINT
4350 PRINT "Best fit constants"
4360 FOR I=1 TO N9
4370   PRINT A1[I,I7]
4380 NEXT I
4390 RETURN
```

****

>>>>>>>>>>>>>>>>MCMUTL<<<<<<<<<<<<<<<<<<

```
  10 DIM N1$[10],N2$[10],A[10,10],A1[30,30],V[10],Z3[10]
  20 DIM X[26],K$[26,3],D[30,10],Y4[30,10]
  30 DIM Y5[30],D1[30],D2[30]
  40 DIM N3$[10]
```

```
 50 DIM F$[10]
 60 FILES *,*
 70 DATA "k01","k10","k12","k21","k20"
 80 DATA "k23","k32","k30","k24","k42","k40"
 90 DATA "k25","k52","k50","k26","k62","k60"
100 DATA "k27","k72","k70","k28","k82","k80"
110 DATA "k29","k92","k90"
120 INPUT "Explanation? Y/N ",F$
130 IF F$="Y" THEN GOSUB 3850
140 INPUT "Read(R), Write, convert or add noise(W), End(/) ",F$
150 MAT READ K$
160 RESTORE
170 Z1=0
180 IF F$="W" THEN 1310
190 IF F$="/" THEN END
200 INPUT "File name (input or new file) ",N1$
210 ASSIGN N1$,1,F1
220 IF F1=0 THEN 270
230 IF F1=3 THEN PRINT "File does not exist"
240 INPUT "Try again (/) or go one step back ",F$
250 IF F$="/" THEN 200
260 GOTO 140
270 READ #1;N1,N,N4
280 IF N4<>N1 THEN GOSUB 2710
290 IF N4<>N1 THEN PRINT " *** Dual hepato data ***"
300 IF N4<>N1 THEN N5=N+1
310 IF N4=N1 THEN N5=N
320 N9=5+(N1-2)*3
330 PRINT "Number of compartments ";N1
340 IF N<>N1 THEN PRINT "UPTAKE"
350 IF N=N1 THEN PRINT "EXCRETION"
360 REDIM A[N,N],V[N1],Z3[N],X[N9],A1[N9+1,N9+1]
370 IF TYP(1)=3 THEN 140
380 IF TYP(1)=2 THEN READ #1;F$
390 IF LEN(F$)=1 THEN 420
400 ADVANCE #1;1,V1
410 GOTO 370
420 IF F$="V" THEN GOSUB 510
430 IF F$="Z" THEN GOSUB 550
440 IF F$="W" THEN GOSUB 650
450 IF F$="X" THEN GOSUB 680
460 IF F$="D" THEN GOSUB 730
470 IF F$="S" THEN GOSUB 980
480 IF F$="R" THEN GOSUB 1230
490 IF F$="C" THEN GOSUB 1270
500 GOTO 370
510 MAT READ #1;V
520 PRINT "Volumes:"
530 MAT PRINT V
540 RETURN
550 FOR I=1 TO N
555   IF TYP(1)=1 THEN 560
556   Z3[I]=0
557   GOTO 580
560   READ #1;Z3[I]
570 NEXT I
580 IF TYP(1)=2 THEN 620
```

```
590 ADVANCE #1;1,V1
600 PRINT "!!!!!!!!!! FILE WITH FLIPPED CONSTANTS !!!!!!!!!!!!!!!!!"
610 PRINT "Data do not apply"
620 PRINT "Initial concentrations (water last)"
630 MAT PRINT Z3
640 RETURN
650 READ #1;K
660 PRINT "Rate constant for concentration decrease in water ",K
670 RETURN
680 MAT READ #1;X
690 FOR I=1 TO N9
700   PRINT K$[I],X[I]
710 NEXT I
720 RETURN
730 READ #1;N2
740 REDIM D[N2,N1+1],Y4[N2,N1],D1[N2],D2[N2]
750 MAT READ #1;D
760 PRINT "Time                Concentration                "
770 PRINT "-------------------------------------------------"
780 FOR I=1 TO N1
790   PRINT TAB(7);I;
800 NEXT I
810 PRINT
820 PRINT "-------------------------------------------------"
830 FOR I=1 TO N2
840   FOR J=1 TO N1+1
850     IF J=1 THEN PRINT USING "#,2D.D";D[I,1]
860     IF J>1 THEN PRINT USING "#,4X,4D.2D";D[I,J]
870   NEXT J
880   PRINT
890 NEXT I
900 PRINT "================================================="
910 IF N4=N1 THEN 970
920 PRINT "Concentration in combined hepato compartment"
930 MAT READ #1;D1
940 FOR I=1 TO N2
950   PRINT D1[I]
960 NEXT I
970 RETURN
980 READ #1;C9
990 MAT READ #1;A1
1000 MAT READ #1;Y4
1010 IF N1=N4 THEN 1030
1020 MAT READ #1;D2
1030 PRINT "Number of iterations ",C9
1040 PRINT "Simplex status "
1050 MAT PRINT A1
1060 PRINT "Time              Concentration ( Data <-> Calculated)"
1070 PRINT "-------------------------------------------------"
1080 FOR I=1 TO N2
1090   FOR J=1 TO N1+1
1100     IF J=1 THEN PRINT USING "#,2D.D";D[I,1]
1110     IF J=1 THEN 1130
1120     PRINT USING "#,3X,4D.2D,2X,4D.2D";D[I,J],Y4[I,J-1]
1130   NEXT J
1140   PRINT
1150 NEXT I
```

```
1160 PRINT "-------------------------------------------------------"
1170 IF N1=N4 THEN 1260
1180 PRINT "Concentration in combined hepato (Data<->Calculated)"
1190 FOR I=1 TO N2
1200   PRINT D1[I];D2[I]
1210 NEXT I
1220 RETURN
1230 READ #1;E
1240 READ #1;N2$
1250 PRINT "Noise at ";E;"% ";"Added to file ";N2$
1260 RETURN
1270 READ #1;N1$,N2$,X
1280 PRINT "File ";N2$;" was obtained by conversion from file ";N1$
1290 PRINT "       by using ";X;" as fraction in original hepato."
1300 RETURN
1310 REM ***** WRITE FILE **************
1320 INPUT "File name (input or new file) ",N1$
1330 CREATE Z,N1$,200
1340 IF Z=0 THEN 1420
1350 IF Z=1 THEN 1380
1360 PRINT "File not created"
1370 GOTO 1320
1380 PRINT "FILE EXISTS!"
1390 INPUT &
   "Add noise(1),convert(2),flip constants(UPT/EXCR)[3],quit(4) ",Z1
1400 IF Z1=4 THEN 140
1410 D$="N"
1420 ASSIGN N1$,1,Z
1430 IF Z=0 THEN 1460
1440 PRINT "SOMETHING WRONG WITH FILE"
1450 GOTO 140
1460 IF Z1<>3 THEN 1550
1470 READ #1;N1,N
1480 IF N>N1 THEN 1510
1490 N=N+1
1500 GOTO 1520
1510 N=N-1
1520 ADVANCE #1;-1,Z
1530 UPDATE #1;N
1540 GOTO 140
1550 IF Z1=2 THEN 2750
1560 IF D$="N" THEN 2210
1570 PRINT "Operation:"
1580 INPUT "Write Constants(C), Data (D) ",D$
1590 IF D$="D" THEN 1610
1600 INPUT "Dual hepato? Y/N ",D1$
1610 INPUT "Uptake (1), Excretion (2) ",Q3
1620 IF D$="D" THEN 1680
1630 IF D1$="N" THEN 1680
1640 GOSUB 2710
1650 N1=5
1660 N4=0
1670 GOTO 1700
1680 INPUT "Number of compartments ",N1
1690 N4=N1
1700 N=N1+1
1710 N9=5+(N1-2)*3
```

```
1720 IF Q3=2 THEN N=N1
1730 PRINT #1;N1,N,N4
1740 REDIM A[N,N],V[N1],X[N9],Z3[N]
1750 IF D$="C" THEN 2010
1760 PRINT "Compartment volumes"
1770 PRINT #1;"V"
1780 FOR I=1 TO N1
1790   PRINT I,
1800   INPUT V[I]
1810   PRINT #1;V[I]
1820 NEXT I
1830 PRINT "Initial concentrations (water last)"
1840 PRINT #1;"Z"
1850 FOR I=1 TO N
1860   IF Q3=2 THEN 1900
1870   IF I<>N THEN PRINT "Compartment ";I,
1880   IF I=N THEN PRINT "Water ",
1890   GOTO 1910
1900   PRINT "Compartment ",I,
1910   INPUT Z3[I]
1920   PRINT #1;Z3[I]
1930 NEXT I
1940 PRINT #1;"W"
1950 IF N<>N1 THEN 1980
1960 PRINT #1;0
1970 GOTO 2000
1980 INPUT "Rate of exponential decrease in Cw ",K
1990 PRINT #1;K
2000 IF D$="D" THEN 2070
2010 PRINT #1;"X"
2020 FOR I=1 TO N9
2030   PRINT K$[I],
2040   INPUT X[I]
2050   PRINT #1;X[I]
2060 NEXT I
2070 IF D$="C" THEN 400
2080 PRINT #1;"D"
2090 INPUT "NUMBER OF POINTS ",N2
2100 PRINT #1;N2
2110 REDIM D[N2,N1+1]
2120 FOR I=1 TO N2
2130   FOR J=1 TO N1+1
2140     IF J=1 THEN PRINT "Time"
2150     IF J<>1 THEN PRINT "Concentration in compartment ";J-1
2160     INPUT D[I,J]
2170     PRINT #1;D[I,J]
2180   NEXT J
2190 NEXT I
2200 GOTO 400
2210 INPUT "FILE WITH ADDED NOISE ",N2$
2220 CREATE X,N2$,200
2230 IF X=0 THEN 2250
2240 GOTO 2210
2250 ASSIGN N2$,2,X
2260 READ #1;N1,N,N4
2270 PRINT #2;N1,N,N4
2280 IF N4<>N1 THEN N5=N+1
```

```
2290 IF N4=N1 THEN N5=N
2300 N9=5+(N1-2)*3
2310 REDIM V[N1],Z3[N],X[N9],A1[N9+1,N9+1]
2320 READ #1;F$
2330 MAT READ #1;V
2340 PRINT #2;F$
2350 MAT PRINT #2;V
2360 READ #1;F$
2370 MAT READ #1;Z3
2380 PRINT #2;F$
2390 MAT PRINT #2;Z3
2400 READ #1;F$,C
2410 PRINT #2;F$,C
2420 READ #1;F$
2430 IF F$<>"X" THEN 2480
2440 MAT READ #1;X
2450 PRINT #2;F$
2460 MAT PRINT #2;X
2470 READ #1;F$
2480 READ #1;N2
2490 REDIM D[N2,N1+1]
2500 MAT READ #1;D
2510 PRINT #2;F$,N2
2520 INPUT "RELATIVE ERROR ",E
2530 E=.01*E
2540 FOR I=1 TO N2
2550   FOR J=1 TO N1+1
2560     IF J=1 THEN 2580
2570     D[I,J]=SGN(RND(0)-.5)*RND(0)*E*D[I,J]+D[I,J]
2580   NEXT J
2590 NEXT I
2600 MAT PRINT #2;D
2610 IF N4<>0 THEN 2660
2620 FOR I=1 TO N2
2630   A=(D[I,4]*V[3]+D[I,6]*V[5])/(V[3]+V[5])
2640   PRINT #2;A
2650 NEXT I
2660 PRINT #2;"R",100*E
2670 PRINT #2;N1$
2680 RESTORE #1
2690 RESTORE #2
2700 GOTO 140
2710 K$[12]="k35"
2720 K$[13]="k53"
2730 K$[14]="k50"
2740 RETURN
2750 READ #1;N1,N,N4
2760 IF N1=4 AND N1=N4 THEN 2800
2770 IF N4=0 THEN PRINT "File is dual hepato!"
2780 IF N1<>4 THEN PRINT "Not a 4-compartment file!"
2790 GOTO 140
2800 INPUT "Converted file ",N2$
2810 CREATE Z,N2$,200
2820 IF Z=0 THEN 2850
2830 PRINT "Something wrong with file ";N2$
2840 GOTO 2800
2850 ASSIGN N2$,2,Z
```

```
2860 IF Z=0 THEN 2890
2870 PRINT "File not assigned!"
2880 GOTO 2800
2890 N1=N1+1
2900 N=N+1
2910 N4=0
2920 PRINT #2;N1,N,N4
2930 N9=5+(N1-2)*3
2940 REDIM A[N,N],V[N1],X[N9],Z3[N]
2950 GOSUB 2710
2960 IF TYP(1)=3 THEN 3820
2970 IF TYP(1)=2 THEN READ #1;F$
2980 IF LEN(F$)=1 THEN 3010
2990 ADVANCE #1;1,V1
3000 GOTO 2960
3010 IF F$="V" THEN GOSUB 3080
3020 IF F$="Z" THEN GOSUB 3190
3030 IF F$="W" THEN GOSUB 3440
3040 IF F$="X" THEN GOSUB 3470
3050 IF F$="D" THEN GOSUB 3580
3060 IF F$="R" THEN GOSUB 3770
3070 GOTO 2960
3080 PRINT "Compartment volumes"
3090 FOR I=1 TO N1-1
3100   READ #1;V[I]
3110   PRINT I,V[I]
3120 NEXT I
3130 INPUT "VOLUME OF 2-ND HEPATO COMPARTMENT (COMPARTMENT 5) ",V[5]
3140 V3=V[3]
3150 V[3]=V[3]-V[5]
3160 PRINT #2;"V"
3170 MAT PRINT #2;V
3180 RETURN
3190 PRINT "Initial concentrations "
3200 PRINT #2;"Z"
3210 FOR I=1 TO N1-1
3220   READ #1;Z3[I]
3230   IF I<>3 THEN PRINT I,Z3[I]
3240   IF I=3 THEN PRINT I,Z3[I];"<==="
3250 NEXT I
3260 IF N=N1 THEN 3290
3270 READ #1;Z3[N]
3280 PRINT "Water ",Z3[N]
3290 PRINT "Acceptable initial concentration range"
3300 PRINT "Compartment 3     Compartment 5"
3310 PRINT "-------------------------------------"
3320 A1=Z3[3]*V3/V[3]
3330 A2=0
3340 A3=0
3350 A4=Z3[3]*V3/V[5]
3360 PRINT USING 3370;"X*[",A1,A2,"],","(1-X)*[",A3,A4,"]"
3370 IMAGE 3A,4D.2D,X,D,2A,5X,7A,D,X,4D.2D,A
3380 PRINT "---------------------------------"
3390 INPUT "Fraction in original hepato, X ",X
3400 Z3[3]=X*A1
3410 Z3[5]=(1-X)*A4
3420 MAT PRINT #2;Z3
```

```
3430 RETURN
3440 READ #1;K
3450 PRINT #2;"W",K
3460 RETURN
3470 FOR I=1 TO N9-3
3480   READ #1;X[I]
3490   PRINT K$[I],X[I]
3500 NEXT I
3510 FOR I=N9-2 TO N9
3520   PRINT K$[I],
3530   INPUT X[I]
3540 NEXT I
3550 PRINT #2;"X"
3560 MAT PRINT #2;X
3570 RETURN
3580 READ #1;N2
3590 REDIM D[N2,N1+1],Y4[N2,N1],Y5[N2]
3600 PRINT #2;"D",N2
3610 FOR I=1 TO N2
3620   FOR J=1 TO N1+1
3630     IF J=4 THEN 3670
3640     IF J=6 THEN 3700
3650     READ #1;D[I,J]
3660     GOTO 3710
3670     D[I,J]=0
3680     READ #1;Y5[I]
3690     GOTO 3710
3700     D[I,J]=0
3710   NEXT J
3720 NEXT I
3730 MAT PRINT #2;D
3740 MAT PRINT #2;Y5
3750 PRINT #2;"C",N1$,N2$,X
3760 RETURN
3770 PRINT #2;"R"
3780 READ #1;E,N3$
3790 PRINT #2;E,N3$
3800 RETURN
3810 RETURN
3820 RESTORE #1
3830 RESTORE #2
3840 GOTO 140
3850 PRINT "Utility program for MultiCompartment Model files."
3860 PRINT "There are 3 types of files: CONSTANTS, DATA, and OUTPUT."
3870 PRINT "Constants files contain intercompartment transfer rate"
3880 PRINT "constants and are used in input to MCMSM and to MCMP"
3890 PRINT "(optional). Numbers indicate originating and receiving"
3900 PRINT "compartment, respectively. '0' is water, '1' is the entry"
3910 PRINT "compartment, and '2' is the central compartment. All"
3920 PRINT "compartments are connected to '2' (mammillary model)."
3930 PRINT "Maximum number of compartments is 9."
3940 PRINT &
   "It is possible to have one compartment not connected directly"
3950 PRINT &
   "to the central compartment. This model, referred to as the"
3960 PRINT "'DUAL HEPATO' model consists of 5 compartments, with the"
3970 PRINT &
```

```
    "compartment number 5 connected to the compartment number 3."
 3980 PRINT &
    "Dual hepato files may be written directly or 4-compartment"
 3990 PRINT &
    "mammillary model files may be CONVERTED into dual hepato files."
 4000 PRINT "Data files contain compartment volumes and concentrations"
 4010 PRINT "at different times, and are used in input to MCMSM."
 4020 PRINT "Output files from both MCMP and MCMS contain calculated "
 4030 PRINT "concentrations and various other parameters as well and"
 4040 PRINT "may be used in place of data files."
 4050 PRINT &
    "Random noise at specified relative level may be ADDED to data"
 4060 PRINT &
    "files. This is to investigate the effect of 'experimental errors'&
    "
 4070 PRINT "on 'successful' fit. Real data do not need this option."
 4080 FOR I=1 TO 1000 STEP .01
 4090 NEXT I
 4100 RETURN

 ************************************************************

 >>>>>>>>>>>>>>>>>MCMPLT9<<<<<<<<<<<<<<<<<<<<<<

 10 PRINT CHR$(141)
 20 DIM T1(7),T2(7),T3(18),T4(24),U1(7),E1(7),S1(7),S2(7),E(7),K(7),K1(7 )
 30 T1=1
 40 T2=7
 50 DATA 0,.25,.5,1,2,3,4 !UPTAKE TIMES
 60 DATA 0,.5,1,2,3,4,7 !EXCRETION TIMES
 70 DATA .1,.2,.3,.4,.5,.6,.7,.8,1,1.2,1.4,1.6,1.8,2,2.5,3,3.5,4!SPLINE
UPTK
 80 DATA 4.5,5,5.5,6,6.5,7 !SPLINE EXCR ADDITIONAL
 90 FOR I=1 TO 7
 100 READ T1(I)
 110 NEXT I
 120 FOR I=1 TO 7
 130 READ T2(I)
 140 T2(I)=T2(I)+4 !PLOTTING OFFSET
 150 NEXT I
 160 FOR I=1 TO 18
 170 READ T3(I)
 180 NEXT I
 190 RESTORE 70
 200 FOR I=1 TO 24
 210 READ T4(I)
 220 T4(I)=T4(I)+4
 230 NEXT I
 240 PLOTR
 250 LORG (5)
 260 LOCATE (100,190,7,99)
 270 INPUT "1.Gills, 2.Blood, 3.Hepato , 0. End ",T
 280 IF T=0 THEN 1170
 290 IF T=1 THEN Y2=3600
 300 IF T=2 THEN Y2=1200
 310 IF T=3 THEN Y2=1000
```

```
320 PRINT CHR$(141)
330 FRAME
340 SCALE (0,12,0,Y2)
350 IF T=1 THEN MOVE (1,3400)\ PRINT #0;"Gills"
360 IF T=2 THEN MOVE (1,1000)\ PRINT #0;"Blood"
370 IF T=3 THEN MOVE (1,800)\ PRINT #0;"Hepato"
380 LAXES (-1,200,0,0,1,1,2)
390 LINE (2)
400 MOVE (4,Y2)
410 DRAW (4,0)
420 LINE (0)
430 IF T=2 THEN RESTORE 500
440 IF T=3 THEN RESTORE 540
450 DATA 111,670,630,961,1823,1905,2510  !UPTAKE GILLS
460 DATA 2510,2038,1600,1871,1046,843,675!EXCRETION GILLS
470 DATA 21,327,61,172,328,803,954       !SD UPTAKE GILLS
480 Y=Y
490 DATA 954,441,444,719,240,215,181     !SD EXCRETION GILLS
500 DATA 90,162,200,337,655,650,753 !UPTAKE BLOOD
510 DATA 753,817,770,693,598,544,430 !EXCRETION BLOOD
520 DATA 38,36,55,44,195,204,256 !SD UPTAKE BLOOD
530 DATA 256,230,209,171,144,89,213 !SD EXCRETION BLOOD
540 DATA 104,110,105,213,234,320,734 !UPTAKE HEPATO
550 DATA 734,705,544,573,697,489,603 !EXCRETION HEPATO
560 DATA 28,46,64,122,109,211,82 !SD UPTAKE HEPATO
570 DATA 82,287,188,119,253,95,344 !SD EXCRETION HEPATO
580 DATA 214,312,408,503,596,687,774,860,1026,1184,1337,1484,1625,1761
590 DATA 2082,2384,2677,2695 !GILLS UPTAKE SPLINE
600 DATA 2010,1978,1945,1913,1880,1848,1816,1784,1720,1657,1594,1533
610 DATA 1473,1414,1274,1146,1034,938,859,794,740,695,656,619!GLS EX SP
620 DATA 118,143,167,191,215,240,264,288,336,382,427,469,509,546,623
630 DATA 687,742,796 !BLOOD SPLINE UPTK
640 DATA 799,793,787,780,774,768,762,756,743,731,719,706,694,682,651
650 DATA 620,589,558,528,497,466,435,404,373 !BLOOD SPLINE EXCR
660 DATA 85,96,107,118,129,141,152,164,188,212,238,265,293,323,403
670 DATA 493,589,689 !HEPATO UPTK SPLINE
680 DATA 668,664,660,656,651,647,643,639,631,623,615,607,599,591,572
690 DATA 553,535,518,501,485,469,453,438,423!HEPATO EXCR SPLINE
700 FOR I=1 TO 7
710 READ U1(I)
720 NEXT I
730 FOR I=1 TO 7
740 READ E1(I)
750 NEXT I
760 FOR I=1 TO 7
770 READ S1(I)
780 NEXT I
790 FOR I=1 TO 7
800 READ S2(I)
810 NEXT I
820 FOR I=1 TO 7
830 X=T1(I)
840 Y=U1(I)
850 Y1=U1(I)+S1(I)
860 Y3=U1(I)-S1(I)
870 GOSUB 1120
880 NEXT I
```

```
890 FOR I=1 TO 7
900 X=T2(I)
910 Y=E1(I)
920 Y1=E1(I)+S2(I)
930 Y3=E1(I)-S2(I)
940 GOSUB 1120
950 NEXT I
960 IF T=1 THEN RESTORE 580
970 IF T=2 THEN RESTORE 620
980 IF T=3 THEN RESTORE 660
985 !************************ PLOTTING SPLINES **********************
990 FOR I=1 TO 18
1000 READ A
1010 MOVE (T3(I),A)
1020 PRINT #0;"x"
1030 NEXT I
1040 FOR I=1 TO 24
1050 READ A
1060 MOVE (T4(I),A)
1070 PRINT #0;"x"
1080 NEXT I
1090 PENUP
1091 !************************************************************
1095 Y1=0
1100 GOTO 1180
1110 GOTO 270
1115 !********************* PLOTTING MEANS & SD'S ********************
1120 MOVE (X-.1,Y)
1130 DRAW (X+.1,Y)
1140 MOVE (X,Y1)
1150 DRAW (X,Y3)
1160 RETURN
1165 !************************************************************
1170 END
1180 RESTORE 2010 !<===== DATA POINTER !!!!!!!!!!!!!!!!!!!!!!!!
1190 I1=0
1195 !PRINT "Eigenvalues" !<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
1200 FOR I=1 TO 6
1210 READ E(I)     ! EIGENVALUES.Number of nonzero eigenvalues equals
1215 !PRINT E(I) !<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
1220 IF E(I)=0 THEN 1240 !the number of compartments
1230 NEXT I
1240 I1=I-1
1250 IF I1=5 THEN READ V3,V5 !Must be dual hepato
1260 !PRINT V3,V5
1270 IF T=2 THEN RESTORE 2030!<====== DATA POINTER !!!!!!!!!!!!!!!
1280 IF T=3 THEN RESTORE 2040!<====== DATA POINTER !!!!!!!!!!!!!!!!
1290 I2=0
1300 FOR I=1 TO 7
1310 READ K(I)
1320 !PRINT K(I) !<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
1330 IF K(I)=0 THEN 1350
1340 NEXT I
1350 I2=I-1
1360 !PRINT I1
1370 IF I1=5 AND T=3 THEN 1390
1380 GOTO 1420
```

```
1390 FOR I=1 TO I2   !Read constants for compartment 5 in dual hepato
1400 READ K1(I)! PRINT K1(I) <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
1410 NEXT I
1420 T1=4\T2=7
1430 !PRINT "I1 ";I1,"I2 ";I2
1440 IF I1<I2 THEN T1=0      !Uptake
1450 IF I1<I2 THEN T2=4      !Excretion
1460 I3=0  !Flag to print every 5-th value
1470 FOR I=0 TO T2 STEP .1
1480 Y,Y1=0
1490 FOR J=1 TO I1
1500 IF I1=5 AND T=3 THEN 1520
1510 GOTO 1530
1520 Y1=Y1+K1(J)*EXP(E(J)*I)
1530 Y=Y+K(J)*EXP(E(J)*I)
1535 !PRINT "***";I,Y,Y1
1540 NEXT J
1545 !PRINT "1545    ",Y,Y1
1550 IF T1=4 THEN 1600
1560 Y=Y+K(I1+1)    !The 'nonexponetial' term in uptake
1570 IF I1=5 AND T=3 THEN 1590
1580 GOTO 1600
1590 Y1=Y1+K1(I1+1)
1595 !PRINT "1595    ",Y,Y1
1600 IF I1=5 AND T=3 THEN 1620
1610 GOTO 1630
1620 Y=(V3*Y+V5*Y1)/(V3+V5)
1630 PLOT (T1+I,Y)
1640 IF I3=0 OR I3=5 THEN 1660
1650 GOTO 1680
1660 !PRINT T1+I,Y !<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
1670 I3=0
1680 I3=I3+1
1690 NEXT I
1700 PENUP
1710 IF T1=0 THEN 1300
1720 GOTO 1110
1725 !^^^^^^^^^^^^^^^^ DATA SET ^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^
1730 DATA -1.99157,-.765031,-.116129,-6.27669E-3,-4.99894E-5,0!EGNVAL
1740 DATA 6.48,2 !VOLUMES OF COMPARTMENTS 3 AND 5
1750 DATA -794.615,-1024.3,-909.471,-376.203,-.31103,3215.9,0!COMP1 upt
1760 DATA 7611.382,1092.94,362.588,12.0689,2.40747E-2,0 !COMP1 excr
1770 ! terminate by 0 !!
1780 DATA 264.326,-476.209,-806.574,-360.513,-.299317,1469.27,0!CMP2 uP
1790 DATA -253.272,508.118,321.565,11.5656,2.31681E-2,0 !COMP2 excr
1800 DATA-101.212,652.9122,-2961.791,-1583.9,-.817605,4008.41,0!CMP3 UP
1810 DATA 8.27446,-140.089,4521.03,-68915.2,-13.3141,64936.3 !COMP5 upt
1820 DATA 96.9792,-696.662,1180.81,50.8131,6.32851E-2,0 !COMP3 excr
1830 DATA -7.9284,149.476,-1802.44,2210.86,1.0305 !COMP5 excr
1835 !^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^
2000 !^^^^^^^^^^^^^^^^^^ DATA SET SBRM 342 ^^^^^^^^^^^^^^^^^^^^^^^^^
2010 DATA -3.32784,-1.75205,-8.01932E-2,-1.91415E-3,0 !EIGENVALUES <--
2020 DATA -491.428,-851.523,-1996.56,-94.1809,3544.69,0 !COMP1 UPT
2025 DATA 501.435,876.111,620.615,1.8389,0!COMP1 EXCR
2030 DATA 210.387,-289.843,-2307.48,-112.443,2589.38,0!COMP2 UPT <-----
2035 DATA -214.671,298.212,717.263,2.19547,0!COMP2 EXCR
2040 DATA -77.7317,284.335,-2994,-131.587,3022.98,0!COMP3 UPT <-------
```

```
2045 DATA 79.3145,-292.546,930.662,2.56926,01COMP3 EXCR
2050 !^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^
2100 !^^^^^^^^^^^^^^^^^^^^ DATA SET SBRDM1&2 ^^^^^^^^^^^^^^^^^^^^
2110 DATA -6.01461,-2.30475,-.368875,-2.23497E-2,-3.45481E-3,01EIGVAL
2115 DATA 6.48,2 !V3,V5 COMPARTMENT VOLUMES
2120 DATA -413.676,-81.0881,-1641.55,-1058.66,-87.0793,3393.06,01CMP1 UP
2125 DATA 392.138,96.7326,1367.72,103.78,3.62652,01COMP1 EXCR
2130 DATA 93.2218,-29.6414,-1106.22,-771.845,-63.7497,1968.23,01CMP2 UP
2135 DATA -88.3681,35.3602,921.689,75.664,2.65493,01COMP2 EXCR
2140 DATA -14.1358,85.0642,-352.971,-608.657,-31.6475,935.957,01CMP3 UP
2150 DATA 6.3161,-100.85,3049.4,-41940.5,-1464.13,40846.6,01COMP5 UPT
2155 DATA 13.3998,-101.476,294.091,59.6668,1.318,01COMP3 EXCR
2160 DATA -5.98725,120.307,-2540.73,4111.43,60.976,01COMP5 EXCR
2170 !^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^
2200 !^^^^^^^^^^^^^^^^^^^^^^ DATASET FSBR, EXCRETION CONSTS ^^^^^^^^^^
2210 DATA -2.43291,-.95892,-7.42137E-2,-3.60439E-5,01EIGENVALUES <----
2220 DATA -24.2796,-2425.61,-1783.61,-.211948,4344.71,01COMP1 UPT
2225 DATA 36.811,1624.13,1304.01,5.59691E-2,01COMP1 EXCR
2230 DATA 25.9794,-1.22286,-1146.93,-.14771,1212.32,01COMP2 UPT  <----
2235 DATA -39.3882,.818852,838.53,3.90056E-2,01COMP2 EXCR
2240 DATA -14.0445,144.702,-1045.76,-.124187,1019.23,01COMP3 UPT <----
2245 DATA 21.2933,-96.8889,764.563,3.7941E-2,01COMP3 EXCR
2250 !^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^
```